



(19)

Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) EP 0 796 243 B1

(12)

## EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention  
of the grant of the patent:  
27.01.1999 Bulletin 1999/04

(51) Int Cl. 6: C07C 255/60, A61K 31/275,  
C07C 271/24, C07D 217/22,  
A61K 31/44, C07D 213/74

(21) Application number: 95935742.7

(86) International application number:  
PCT/US95/13125

(22) Date of filing: 03.10.1995

(87) International publication number:  
WO 96/15103 (23.05.1996 Gazette 1996/23)

### (54) DIAMINOCYCLOBUTENE-3,4-DIONES

DIAMINOCYCLOBUTEN-3,4-DIONE

DIAMINOCYCLOBUTENE-3,4-DIONES

(84) Designated Contracting States:  
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT  
SE

• BUTERA, John, Anthony  
Clarksburg, NJ 08510 (US)  
• HIRTH, Bradford, Hammond  
Littleton, MA 01460 (US)  
• ANTANE, Schuyler, Adam  
Lawrenceville, NJ 08648 (US)

(30) Priority: 16.11.1994 US 340697  
02.06.1995 US 459598  
02.06.1995 US 460170

(74) Representative: Connelly, Michael John  
c/o Patent Department  
Wyeth Laboratories  
Huntercombe Lane South  
Taplow  
Maidenhead Berkshire SL6 0PH (GB)

(43) Date of publication of application:  
24.09.1997 Bulletin 1997/39

(56) References cited:  
EP-A- 0 426 379 US-A- 5 354 763

(73) Proprietor: AMERICAN HOME PRODUCTS  
CORPORATION  
Madison, New Jersey 07940-0874 (US)

• LIEBIGS ANN. CHEM, no. 1, 1973 pages 619-632,  
E. NEUSE ET AL. 'Amidierung von  
Quadratsäure-estern' cited in the application

(72) Inventors:  
• ANTANE, Madelene, Miyoko  
Lawrenceville, NJ 08648 (US)

EP 0 796 243 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

**Description**

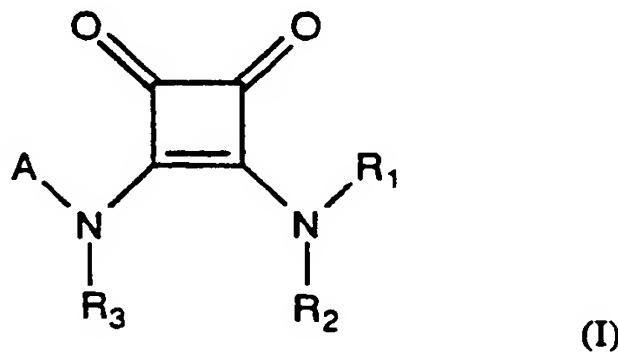
The present invention relates to novel 1, 2-diamino derivatives of cyclobutene 3,4-diones having pharmacological activity, to a process for their preparation, to pharmaceutical compositions containing them, and to their use in the treatment of disorders associated with smooth muscle contraction; via potassium channel modulation. Such disorders include, but are not limited to: urinary incontinence, hypertension, asthma, premature labor, irritable bowel syndrome, congestive heart failure, angina, and cerebral vascular disease.

5 Stemp et al. disclose a class of amino substituted cyclobutenedione derivatives of chromans described as having blood pressure lowering activity and bronchodilatory activity in EP-426379-A2. The compounds are also of potential 10 use in the treatment of disorders associated with smooth muscle contraction of the gastro-intestinal tract, respiratory system, uterus or urinary tract.

15 Butera et al disclose substituted N-heteroaryl and N-aryl-1,2-diaminocyclobut-3,4-diones as muscle smooth relaxants in US Patent 5,354,763. The compounds of the present invention differ in that they are N-acylated.

20 Several series of 1-amino-2-phenylalkylamino-cyclobutene-3,4-diones are reported as H-2 receptor antagonists by Algieri et al. in US Patent 4,390,701. Several related 1-amino-2-phenoxyalkylamino derivatives are disclosed by Nohara et al. in US Patent 4,673,747.

25 The syntheses of variously substituted 1,2-diamino-cyclobutene-3,4-diones are described in the following publications: Tietze et al., *Chem Ber.* 1991, 124, 1215; Tietze et al., *Bioconjugate Chem.* 1991, 2, 148; Ehrhardt et al., *Chem. Ber.* 1977, 110, 2506, and Neuse et al., *Liebigs Ann. Chem.* 1973, 619. For example, Neuse et al. discloses 30 1-phenylamino-2-dimethylamino-cyclobut-1-ene-3,4-dione. The compounds of the present invention differ from the Neuse et al. compound in that they are N-acylated and they are useful as smooth muscle relaxants.



40 wherein:

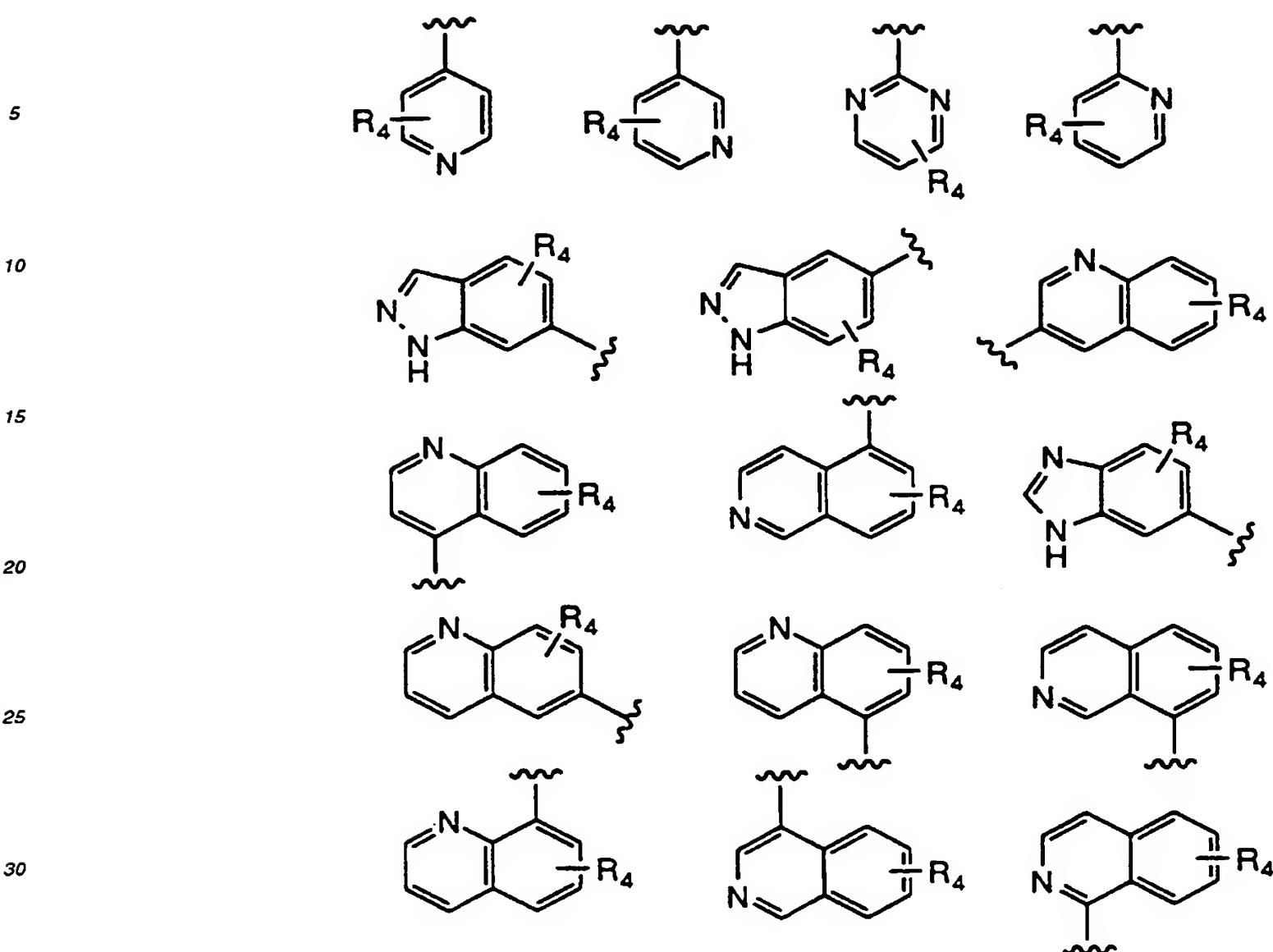
R<sub>1</sub> and R<sub>2</sub> are, independent from each other, hydrogen, C<sub>1-10</sub> straight chain alkyl, C<sub>1-10</sub> branched alkyl, or C<sub>3-10</sub> cyclic or bicyclic alkyl;

R<sub>3</sub> is an acyl substituent selected from the group consisting of formyl, alkanoyl of 2 to 7 carbon atoms, alkenoyl of 3 to 7 carbon atoms, alkylsulfonyl of 1 to 7 carbon atoms, aroyl of 7 to 12 carbon atoms, arylalkenoyl of 9 to 20 carbon atoms, arylsulfonyl of 6 to 12 carbon atoms, arylalkanoyl of 8 to 12 carbon atoms or arylalkylsulfonyl of 7 to 12 carbon atoms;

A is selected from the group consisting of:

50

55



35 wherein:

$R_4$  is hydrogen,  $C_{1-6}$  alkyl,  $C_{1-6}$  perfluoroalkyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  perfluoroalkoxy, amino,  $C_{1-6}$  alkylamino,  $C_{2-12}$  dialkylamino,  $C_{1-6}$  alkylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, nitro, cyano, carboxyl;

40 or, A is a phenyl group of the following formula:



50 wherein:

$R_5$  and  $R_6$ , independent from each other, are selected from the following: cyano, nitro, amino,  $C_{1-6}$  alkyl,  $C_{1-6}$  perfluoroalkyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  perfluoroalkoxy,  $C_{1-6}$  alkylamino,  $C_{2-12}$  dialkylamino, sulfamyl,  $C_{1-6}$  alkylsulfonamido,  $C_{6-12}$  arylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, arylcarboxamido containing 7 to 13 carbon atoms,  $C_{2-6}$  alkanoyl,  $C_{1-6}$  alkylsulfonyl,  $C_{1-6}$  perfluoroalkylsulfonyl,  $C_{6-12}$  arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl or hydrogen;

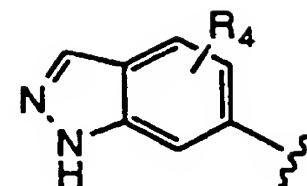
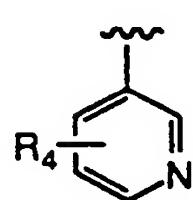
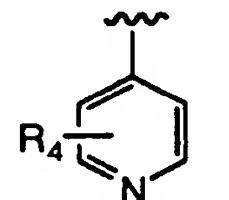
or a pharmaceutically acceptable salt thereof.

A preferred aspect of this invention includes compounds of formula (I) wherein:

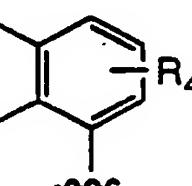
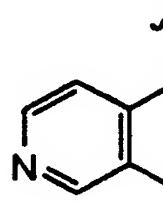
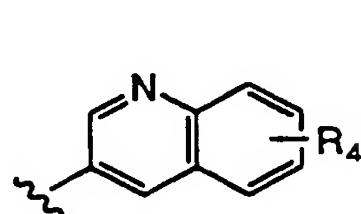
5 R<sub>1</sub> and R<sub>2</sub> are as stated above;

A is selected from the following:

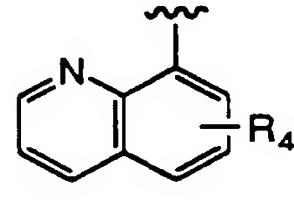
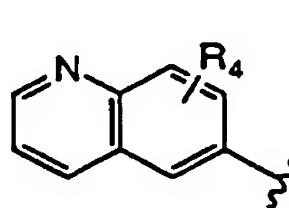
10



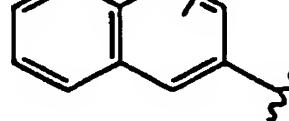
15



20



25



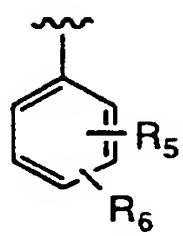
30

wherein:

R<sub>4</sub> is as stated above;

or, A is a phenyl group of the following formula:

35



40

45

wherein:

R<sub>5</sub> and R<sub>6</sub>, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, perfluoroalkyl of 1 to 6 carbon atoms, alkanoyl of 2 to 6 carbon atoms, carboxyl or hydrogen;

50

or a pharmaceutically acceptable salt thereof.

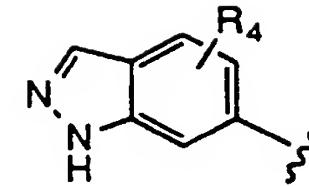
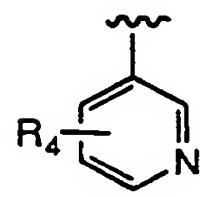
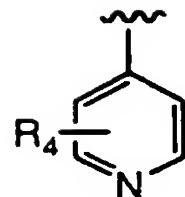
The most preferred aspect of this invention includes compounds of formula (I) wherein:

55

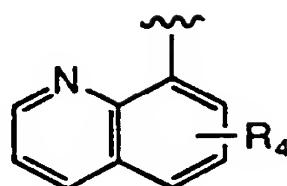
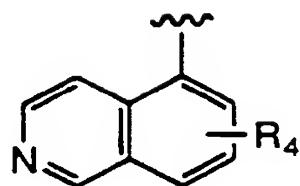
R<sub>1</sub> and R<sub>2</sub> are as stated above;

A is selected from the following:

5



10



15

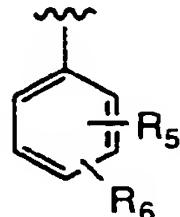
wherein:

R<sub>4</sub> is as stated above;

20

or, A is a phenyl group of the following formula:

25



30

wherein:

R<sub>5</sub> and R<sub>6</sub>, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, perfluoroalkyl of 1 to 6 carbon atoms, alkanoyl of 2 to 6 carbon atoms, carboxyl or hydrogen;

or a pharmaceutically acceptable salt thereof.

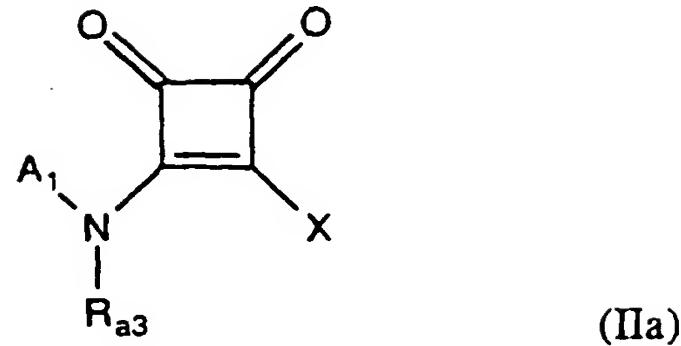
It is understood that the definition of the compounds of formula (I), when R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, or R<sub>5</sub> contain asymmetric carbons, encompass all possible stereoisomers and mixtures thereof which possess the activity discussed below. In particular, it encompasses racemic modifications and any optical isomers which possess the indicated activity. Optical isomers may be obtained in pure form by standard separation techniques or enantiomer specific synthesis. The compounds of this invention, throughout this specification, are equivalently name as 3,4-diones or 1,2-diones. The pharmaceutically acceptable salts of the basic compounds of this invention are those derived from such organic and inorganic acids as: lactic, citric, acetic, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids. Where R<sub>3</sub>, R<sub>4</sub>, or R<sub>5</sub> is a carboxyl group, salts of the compounds of this invention may be formed with bases such as alkali metals (Na, K, Li) or the alkaline earth metals (Ca or Mg).

The present invention also provides a process for the preparation of a compound of formula (I). More particularly, the compounds of formula (I) may be prepared by reacting a compound of formula (IIa):

50

55

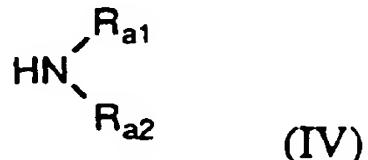
5



10

15 wherein X is a leaving group, for example, methoxy, ethoxy, isopropoxy, halogen or a similar leaving group and A<sub>1</sub> is A and R<sub>a3</sub> is R<sub>3</sub>, as defined hereinbefore or a group of atoms convertible thereto, with a compound of formula (IV):

20

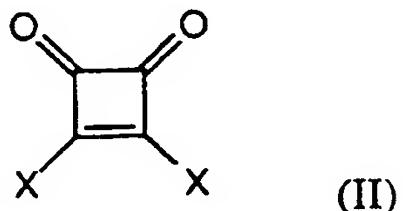


25 wherein R<sub>a1</sub> and R<sub>a2</sub> are R<sub>1</sub> and R<sub>2</sub>, respectively, as defined hereinbefore or a group of atoms convertible thereto and, where appropriate, converting A<sub>1</sub> into A or converting R<sub>a1</sub> into R<sub>1</sub> or converting R<sub>a2</sub> into R<sub>2</sub>, followed by reacylation if necessary and, where desired, converting a compound having formula (I) into a pharmaceutically acceptable salt thereof or converting a salt of a compound having formula (I) into a compound having formula (I).

The compounds having formula (IIa) may be prepared by reaction of a compound of formula (II):

30

35



40 where X is as defined above with a compound of formula (III):



45 wherein A<sub>1</sub> is as defined above, followed by acylation to provide R<sub>a3</sub>. Of course, acylation may also be conducted after reaction of the A<sub>1</sub> substituted compound with HNR<sub>a1</sub>R<sub>a2</sub>.

The reactions mentioned above may be carried out in a solvent such as acetonitrile, methanol or ethanol at elevated or ambient temperatures.

50 As mentioned previously, the compounds of formula (I) and their pharmaceutically acceptable salts have been found to relax smooth muscle. They are therefore useful in the treatment of disorders associated with smooth muscle contraction, disorders involving excessive smooth muscle contraction of the urinary tract (such as incontinence), or of the gastro-intestinal tract (such as irritable bowel syndrome), asthma, and hair loss. Furthermore, the compounds of formula (I) are active as potassium channel activators which render them useful for treatment of peripheral vascular disease, hypertension, congestive heart failure, stroke, anxiety, cerebral anoxia and other neurodegenerative disorders.

55 The present invention accordingly provides a pharmaceutical composition which comprises a compound of this invention in combination or association with a pharmaceutically acceptable carrier. In particular, the present invention

provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example, parenteral administration for patients suffering from heart failure.

In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. Suitable unit dose forms include tablets, capsules and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 100 mg of a compound of the invention and preferably from 2 to 50 mg. Still further preferred unit dosage forms contain 5 to 25 mg of a compound of the present invention. The compounds of the present invention can be administered orally at a dose range of about 0.01 to 100 mg/kg or preferably at a dose range of 0.1 to 10 mg/kg. Such compositions may be administered from 1 to 6 times a day, more usually from 1 to 4 times a day.

The compositions of the invention may be formulated with conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavoring agent and the like. They are formulated in conventional manner, for example, in a manner similar to that used for known antihypertensive agents, diuretics and  $\beta$ -blocking agents.

The present invention further provides a compound of the invention for use as an active therapeutic substance.

Compounds of formula (I) are of particular use in the induction of smooth muscle relaxation.

The present invention further provides a method of treating smooth muscle disorders in mammals including man, which comprises administering to the afflicted mammal an effective amount of a compound or a pharmaceutical composition of the invention.

The following examples are presented to illustrate rather than limit the methods for production of representative compounds of the invention.

### EXAMPLE 1

#### N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-propionamide

4-Aminobenzonitrile (17.58 g, 149 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (25.31 g, 149 mmol) in absolute ethanol (450 mL). The mixture was heated at reflux overnight and the resulting suspension filtered hot to remove a small amount of a dirty yellow solid (discarded). The filtrate was gradually concentrated to afford several crops of 4-(3,4-dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile, as a bright yellow solid, which were collected by filtration and combined. Yield: 29.11 g (81%):  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  11.07 (s, 1H), 7.81 (d, 2H), 7.56 (d, 2H), 4.79 (q, 2H), 1.46 (t, 3H).

To the product of the preceding paragraph (13.00 g, 53.7 mmol) in ethanol (360 mL) was added 2-amino-3,3-dimethylbutane (7.2 mL, 54 mmol). The mixture was heated at reflux overnight. Gradual concentration of the reaction solution afforded two crops of 4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-benzonitrile, as a yellow precipitate, which were collected by filtration and combined. Yield: 11.34 g (71%):  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.89 (s, 1H), 7.78 (d, 2H), 7.72 (d, 1H), 7.60 (d, 2H), 3.96 (m, 1H), 1.18 (d, 3H), 0.91 (s, 9H).

To a solution of the product of preceding paragraph (1.20 g, 4.04 mmol) in N,N-dimethylformamide (36 mL) was added, in one portion, sodium hydride (as a 60% dispersion in mineral oil; 0.179 g, 4.48 mmol). The frothy suspension was stirred at room temperature for 15 minutes and then at 0°C for an additional hour. Propionic anhydride (0.57 mL, 4.45 mmol) was added and the reaction mixture was stirred at 0°C for 15 minutes and then allowed to warm to room temperature. After stirring overnight, the reaction mixture was concentrated. The resulting residue was taken up in methylene chloride and washed with aqueous sodium bicarbonate, brine and water. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford a yellow foam which was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) and trituration ( $\text{Et}_2\text{O}$ ) to afford 0.68 g (48%) of N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-propionamide as a light yellow solid: mp 211-214°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.81 (d, 2H), 7.50-7.42 (m, 3H), 4.28 (m, 1H), 2.18 (m, 2H), 1.26 (d, 3H), 1.10 (t, 3H), 1.00 (s, 9H). IR (KBr): 3330, 2230, 1800, 1740, 1690, 1620  $\text{cm}^{-1}$ ; MS (m/z) 353 ( $\text{M}^+$ ).

Elemental analysis for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3$			
Calc'd	C, 67.97;	H, 6.56;	N, 11.89.
Found	C, 67.77;	H, 6.35;	N, 11.87.

### EXAMPLE 2

#### N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-benzamide

To a solution of the intermediate produced in Example 1, second paragraph (1.20 g, 4.04 mmol) in N,N-dimethyl-

EP 0 796 243 B1

formamide (36 mL) was added, in one portion, sodium hydride (as a 60% dispersion in mineral oil; 0.178 g, 4.45 mmol). The frothy suspension was stirred at room temperature for 15 minutes and then at 0°C for an additional hour. Benzoic anhydride (1.01 mL, 4.46 mmol) was added and the reaction mixture was stirred at 0°C for 15 minutes and then allowed to warm to room temperature. After stirring overnight, the reaction mixture was concentrated. The resulting residue was taken up in methylene chloride and washed with aqueous sodium bicarbonate, brine and water. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford a yellow foam which was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) and trituration (diethyl ether) to afford 0.71 g (44%) of product as a pale yellow solid: mp 229-231°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.61-7.22 (m, 9H), 7.77 (d, 1H), 4.37 (m, 1H), 1.28 (d, 3H), 1.02 (s, 9H). IR (KBr): 3300, 2240, 1790, 1730, 1675, 1610  $\text{cm}^{-1}$ ; MS (m/z) 401 (M $^+$ ).

10

Elemental analysis for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_3$			
Calc'd	C, 71.80;	H, 5.74;	N, 10.47.
Found	C, 71.49;	H, 5.91;	N, 10.18.

15

EXAMPLE 3

N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-methanesulfonamide

20 To a solution of the intermediate of Example 1, second paragraph (1.20 g, 4.04 mmol) in N,N-dimethylformamide (36 mL) was added, in one portion, sodium hydride (as a 60% dispersion in mineral oil; 0.178 g, 4.45 mmol). The frothy suspension was stirred at room temperature for 15 minutes and then at 0°C for an additional hour. Methanesulfonic anhydride (0.82 g, 4.71 mmol) was added and the reaction mixture was stirred at 0°C for 15 minutes and then allowed to warm to room temperature. After stirring overnight, the reaction mixture was concentrated. The resulting residue was taken up in methylene chloride and washed with aqueous sodium bicarbonate, brine and water. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford a yellow foam which was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) and trituration (diethyl ether) to afford 0.71 g (47%) of product as an off-white solid: mp 190-191°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.79 (d, 2H), 7.54 (d, 2H), 6.77 (d, 1H), 4.29 (m, 1H), 3.24 (s, 3H), 1.24 (d, 3H), 0.96 (s, 9H). IR (KBr): 3350, 2220, 1800, 1725, 1610  $\text{cm}^{-1}$ ; MS (m/z) 375 (M $^+$ ).

25

Elemental analysis for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$			
Calc'd	C, 57.58;	H, 5.64;	N, 11.19.
Found	C, 57.60;	H, 5.61;	N, 11.10.

30

EXAMPLE 4

N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-formamide

35 To a solution of the intermediate of Example 1, second paragraph (1.20 g, 4.04 mmol) in N,N-dimethylformamide (36 mL) was added, in one portion, sodium hydride (as a 60% dispersion in mineral oil; 0.178 g, 4.45 mmol). The frothy suspension was stirred at room temperature for 15 minutes and then at 0°C for an additional hour. Trifluoromethanesulfonic anhydride (0.75 mL, 4.46 mmol) was added and the reaction mixture was stirred at 0°C for 15 minutes and then allowed to warm to room temperature. After stirring overnight, the reaction mixture was concentrated. The resulting residue was taken up in methylene chloride and washed with aqueous sodium bicarbonate and water. Recovered starting material, which precipitated as a yellow solid during workup, was filtered away. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford a brown residue which was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ), trituration (diethyl ether) and recrystallization (EtOAc/Hex) to afford 0.12 g (9%) of product as a light yellow solid: mp 187-190°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  10.28 (s, 1H), 8.33 (s, 1H), 7.67 (d, 2H), 7.58 (d, 2H), 5.07 (m, 1H), 1.55 (d, 3H), 1.04 (s, 9H). IR (KBr): 3400, 2220, 1800, 1740, 1690, 1620  $\text{cm}^{-1}$ ; MS (m/z) 325 (M $^+$ ).

40

Elemental analysis for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3$			
Calc'd	C, 66.44;	H, 5.89;	N, 12.91.
Found	C, 66.29;	H, 5.76;	N, 12.74.

45

EXAMPLE 5Hexanoic acid (4-cyano-phenyl)-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-amide

5 To a suspension of the intermediate of Example 1, second paragraph (0.70 g, 2.35 mmol) in pyridine (9 mL) was added hexanoic anhydride (1.50 mL, 6.48 mmol). The mixture was stirred overnight, stripped free of solvent and diluted with diethyl ether. A yellow solid (recovered starting material) which remained undissolved was filtered away. The filtrate was concentrated, dissolved in methylene chloride and stirred vigorously in the presence of an equal volume of dilute aqueous sodium bicarbonate. After 30 minutes the organic layer was removed, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The 10 resulting yellow film was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) to afford 0.43 g (46%) of product as a pale yellow solid: mp 51-65°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.81 (d, 2H), 7.48-7.38 (m, 3H), 4.28 (m, 1H), 2.13 (m, 2H), 1.60 (m, 2H), 1.29-1.13 (m, 7H), 0.99 (s, 9H), 0.86 (t, 3H). IR (KBr): 3340, 2230, 1800, 1725, 1610  $\text{cm}^{-1}$ ; MS (m/z) 395 (M $^+$ ).

15

Elemental analysis for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3$			
Calc'd	C, 69.85;	H, 7.39;	N, 10.62.
Found	C, 69.69;	H, 7.35;	N, 10.50.

EXAMPLE 6N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-isobutyramide

20 To a solution of iso-butyric anhydride (0.42 mL, 2.53 mmol) in pyridine (9 mL) was added the intermediate of Example 1, second paragraph (0.75 g, 2.52 mmol). After stirring overnight additional anhydride (3.8 mL, 22.9 mmol) 25 was added and stirring was continued for a second day. The mixture was stripped free of solvent and diluted with diethyl ether. A yellow solid (recovered starting material) which remained undissolved was filtered away. The filtrate was concentrated and the resulting yellow oil was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) and trituration (diethyl ether) to afford 0.47 g (51%) of product as a pale yellow solid: mp 175-176°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.81 (d, 2H), 7.47 (d, 2H), 7.42 (d, 1H), 4.28 (m, 1H), 2.52 (m, 1H), 1.27 (d, 3H), 1.10 (m, 6H), 1.00 (s, 9H). IR (KBr): 3330, 2230, 1800, 30 1730, 1680, 1610  $\text{cm}^{-1}$ ; MS (m/z) 367 (M $^+$ ).

35

Elemental analysis for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3$			
Calc'd	C, 68.64;	H, 6.86;	N, 11.44.
Found	C, 68.34;	H, 6.75;	N, 11.26.

EXAMPLE 7N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-3-phenyl-acrylamide

40 To a suspension of the intermediate of Example 1, second paragraph (0.50 g, 1.68 mmol) in pyridine (6 mL) was added cinnamic anhydride (0.94 g, 3.38 mmol). After stirring overnight, the mixture was concentrated. The resulting residue was taken up in methylene chloride and washed with aqueous sodium bicarbonate and water. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford a yellow gum which was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) and trituration (diethyl ether) to afford 0.24 g (47%) of product as an off-white solid: mp 235-237°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.80-7.61 (m, 3H), 7.50-7.32 (m, 8H), 6.21 (d, 1H), 4.32 (m, 1H), 1.29 (d, 3H), 1.03 (s, 9H). IR (KBr): 3330, 45 2220, 1800, 1730, 1620, 1600  $\text{cm}^{-1}$ ; MS (m/z) 427 (M $^+$ ).

50

Elemental analysis for $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_3 \cdot (0.06 \text{ CH}_2\text{Cl}_2) \cdot (0.13 \text{ Et}_2\text{O})$			
Calc'd	C, 72.19;	H, 6.02;	N, 9.50.
Found	C, 72.23;	H, 5.96;	N, 9.58.

**EXAMPLE 8****N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-carbamic acid ethyl ester**

5 To a stirred solution of trimethylacetic acid (0.38 g, 3.72 mmol) in tetrahydrofuran (5 mL) at 0°C was added, in order, N,N-diisopropylethylamine (0.65 mL, 3.73 mmol) and (after 10 minutes) ethyl chloroformate (0.36 mL, 3.77 mmol). The resulting suspension of trimethylacetyl ethyl carbonate was stirred for 30 minutes before use in the following step.

10 To a solution of the intermediate of Example 1, second paragraph (1.00 g, 3.36 mmol) in N,N-dimethylformamide (30 mL) was added, in one portion, sodium hydride (as a 60% dispersion in mineral oil; 0.150 g, 3.75 mmol). The frothy suspension was stirred at room temperature for 15 minutes and at 0°C for an additional hour. The mixed anhydride suspension prepared in the preceding paragraph was added all at once. After stirring at room temperature overnight, additional sodium hydride (0.134 g, 3.35 mmol) was added and stirring was continued for a second night. The reaction 15 solution was concentrated and the resulting residue was taken up in methylene chloride and washed with aqueous sodium bicarbonate and water. Unreacted starting material, which precipitated as a yellow solid during workup, was filtered away. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to afford a brown gum which was purified by chromatography ( $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ ) and trituration (diethyl ether) to afford 0.20 g (16%) of N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-carbamic acid ethyl ester as a white solid: mp 158-159°C;  $^1\text{H}$  20 NMR ( $\text{DMSO-d}_6$ ):  $\delta$  8.18 (d, 2H), 7.88 (d, 2H), 7.59 (d, 2H), 4.35-4.07 (m, 3H), 1.23 (t, 3H), 1.19 (d, 3H), 0.91 (s, 9H). IR (KBr): 3340, 2230, 1800, 1720, 1620  $\text{cm}^{-1}$ ; MS (m/z) 369 ( $\text{M}^+$ ).

Elemental analysis for  $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4$ 

Calc'd	C, 65.03;	H, 6.28;	N, 11.37.
Found	C, 64.97;	H, 6.19;	N, 11.17.

**EXAMPLE 9****N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide**

30 The intermediate of Example 1, second paragraph (1.0 g, 3.36 mmol), acetic anhydride (0.95 mL, 10.0 mmol), and pyridine (10 mL) were mixed and allowed to stand at room temperature for 24 hours. The reaction mixture was filtered, and the solid was washed with ethyl acetate yielding 0.84 g (76%) of a yellow solid: mp 284-286°C (dec);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.82 (d, 2H), 7.47 (d, 2H), 7.38 (br d, 1H), 4.27 (dq, 1H), 2.02 (s, 3H), 1.25 (d, 3H), 0.99 (s, 9H). IR (KBr): 3358, 2978, 2236, 1804, 1739, 1685, 1614  $\text{cm}^{-1}$ ; MS (m/z) 339 ( $\text{M}^+$ ).

Elemental analysis for  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_3$ 

Calc'd	C, 67.24;	H, 6.24;	N, 12.38
Found	C, 67.15;	H, 6.19;	N, 12.38

**EXAMPLE 10****(R)-(-)-N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide**

45 4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (1 g, 4.1 mmol) and a solution of (R)-1,2,2-trimethyl-propylamine (8.2 mmol) in ethanol (50 mL) were stirred at room temperature for 24 hours. The resulting yellow slurry was filtered and rinsed with ethyl acetate to yield 0.92 g (75%) of (+)-(R)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-benzonitrile as a yellow solid: spectral data was identical to the product of Example 1, paragraph 50 2, except with  $[\alpha]_D^{25} = +12^\circ$  (DMSO, c 0.009).

50 (R)-(-)-N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide was prepared according to the procedure described in Example 9. From the intermediate of the preceding paragraph (0.22g, 0.74 mmol) and acetic anhydride (0.21 mL, 2.2 mmol) in pyridine (2.2 mL) there was obtained 0.1 g (40%) of a yellow 55 solid: spectral data was identical to the product of Example 9, except with  $[\alpha]_D^{25} = -264^\circ$  (DMSO, c 0.009).

EXAMPLE 11N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-isopropylamino-cyclobut-1-enyl]-acetamide

5      4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (1 g, 4.1 mmol) and isopropylamine (5 g, 84.6 mmol) in acetonitrile (125 mL) were stirred at room temperature for 24 hours. The resulting yellow slurry was filtered to give 0.78 g (31%) of 4-[3,4-dioxo-2-isopropylamino]-cyclobut-1-enylamino]-benzonitrile as a yellow solid: mp 290-292°C (dec);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.89 (br s, 1H), 7.77 (d overlapping a br d, 3H), 7.58 (d, 2H), 4.19 (m, 1H), 1.25 (d, 6H). IR (KBr): 3200, 3178, 2239, 1794, 1665, 1608, 1576, 1524  $\text{cm}^{-1}$ ; MS (m/z) 255 ( $\text{M}^+$ ).

10

Elemental analysis for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$		
Calc'd	C, 65.87; H, 5.13; N, 16.46	
Found	C, 65.39; H, 4.92; N, 16.41	

15

15      N-(4-Cyano-phenyl)-N-[3,4-dioxo-2-isopropylamino]-cyclobut-1-enyl]-acetamide was prepared according to the procedure described in Example 9. From the reactant of the preceding paragraph (0.15 g, 0.59 mmol) and acetic anhydride (0.28 mL, 2.9 mmol) in pyridine (1.8 mL) there was obtained 0.1 g (57%) of pale yellow crystals: mp 187-188°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.82 (d, 2H), 7.45 (d, 2H), 7.22 (br d, 1H), 4.57 (m, 1H), 2.00 (s, 3H), 1.33 (d, 6H). IR (KBr): 3339, 2980, 2239, 1760, 1734, 1695, 1620  $\text{cm}^{-1}$ ; MS (m/z) 297 ( $\text{M}^+$ ).

20

Elemental analysis for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3$		
Calc'd	C, 64.64; H, 5.08; N, 14.13	
Found	C, 64.32; H, 4.83; N, 14.13	

25

EXAMPLE 12N-[2-[Acetyl-(2,2,3,3,3-pentafluoro-propyl)amino]-3,4-dioxo-cyclobut-1-enyl]-N-(4-cyano-phenyl)-acetamide

30

30      4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (1 g, 4.1 mmol) and 2,2,3,3,3-pentafluoropropylamine (3 mL) in ethanol were refluxed for 24 hours. The reaction mixture was filtered and the resulting solid was triturated with diethyl ether to give 1.0 g (71%) of 4-[3,4-dioxo-2-(2,2,3,3,3-pentafluoro-propylamino)-cyclobut-1-enylamino]-benzonitrile as a yellow solid: mp 272-275°C (dec);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.15 (br s, 1H), 8.19 (br s, 1H), 7.81 (d, 2H), 7.79 (d, 2H), 4.54 (dt, 2H). IR (KBr): 3185, 2239, 1804, 1672, 1608, 1565, 1548  $\text{cm}^{-1}$ ; MS (m/z) 346 ( $[\text{M}+\text{H}]^+$ ).

35

Elemental analysis for $\text{C}_{14}\text{H}_8\text{F}_5\text{N}_3\text{O}_2$		
Calc'd	C, 48.71; H, 2.34; N, 12.17	
Found	C, 48.89; H, 2.11; N, 12.21	

40

45      The product of the preceding paragraph (0.13 g, 0.38 mmol), acetic anhydride (0.11 mL, 1.1 mmol), and pyridine (1.1 mL) were mixed and allowed to stand at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate, filtered, and concentrated under reduced pressure. The resulting residue was taken up in hot ethyl acetate and filtered hot. The solution was allowed to cool to room temperature and hexanes was added to aid in the crystallization. The solid was filtered and rinsed sparingly with ethyl acetate to give 0.10 g (63%) of N-[2-[acetyl-(2,2,3,3,3-pentafluoro-propyl)-amino]-3,4-dioxo-cyclobut-1-enyl]-N-(4-cyano-phenyl)-acetamide as a pale yellow solid: mp 187-195°C (dec);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.83 (d, 2H), 7.53 (d, 2H), 4.82 (br m, 2H), 2.37 (s, 3H), 2.07 (s, 3H). IR (KBr): 3435, 2237, 1805, 1772, 1734, 1707, 1603  $\text{cm}^{-1}$ ; MS (m/z) 429 ( $\text{M}^+$ ).

50

Elemental analysis for $\text{C}_{18}\text{H}_{12}\text{F}_5\text{N}_3\text{O}_4$		
Calc'd	C, 50.36; H, 2.82; N, 9.79	
Found	C, 50.62; H, 2.64; N, 9.86	

55

EXAMPLE 13N-(4-Cyano-phenyl)-N-[2-(1,2-dimethyl-propylamino)-3,4-dioxo-cyclobut-1-enyl]-acetamide

5 This compound was prepared according to the procedure described in Example 11, first paragraph. 4-(3,4-Dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (1 g, 4.1 mmol) and ( $\pm$ )-1,2-dimethylpropylamine (5 g, 57.4 mmol) in acetonitrile (125 mL) there was obtained after trituration with methanol 0.28 g (24%) of 4-[2-(1,2-dimethyl-propylamino)-3,4-dioxo-cyclobut-1-enylamino]-benzonitrile as a yellow solid: mp 222-224°C;  $^1$ H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.89 (br s, 1H), 7.78 (d, 2H), 7.73 (d, 1H), 7.59 (d, 2H), 3.98 (m, 1H), 1.76 (m, 1H), 1.19 (d, 3H), 0.90 (d, 3H), 0.89 (d, 3H). IR (KBr): 2980, 2240, 1799, 1660, 1600, 1565, 1525 cm<sup>-1</sup>; MS (m/z) 283 (M<sup>+</sup>).

15

Elemental analysis for C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 67.83;	H, 6.05;	N, 14.83
Found	C, 67.32;	H, 5.94;	N, 14.91

20

N-(4-Cyano-phenyl)-N-[2-(1,2-dimethyl-propylamino)-3,4-dioxo-cyclobut-1-enyl]-acetamide was prepared according to the procedure described in Example 9. From the product of the preceding paragraph (0.27 g, 0.95 mmol) and acetic anhydride (0.27 mL, 2.9 mmol) in pyridine (2.9 mL) there was obtained 0.17 g (55%) of white crystals: mp 258-262°C (dec);  $^1$ H NMR (CDCl<sub>3</sub>):  $\delta$  7.82 (d, 2H), 7.46 (d, 2H), 7.29 (br d, 1H), 4.30 (m, 1H), 2.02 (s, 3H), 1.81 (m, 1H), 1.27 (d, 3H), 1.00 (d, 3H), 0.99 (d, 3H). IR (KBr): 3337, 2967, 2228, 1804, 1739, 1685, 1620 cm<sup>-1</sup>; MS (m/z) 325 (M<sup>+</sup>).

25

Elemental analysis for C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 66.45;	H, 5.87;	N, 12.91
Found	C, 66.48;	H, 5.82;	N, 12.79

30

EXAMPLE 14  
N-(3-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide

35

3-Aminobenzonitrile (2.06 g, 17.4 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (2.97 g, 17.5 mmol) in absolute ethanol (50 mL) was refluxed overnight. The reaction mixture was filtered hot, then allowed to cool to room temperature. The resulting precipitate was filtered to give 3.4 g of a yellow solid which was used without further purification. This yellow solid (1 g, 4.1 mmol) and 2-amino-3,3-dimethylbutane (2 g, 19.8 mmol) in acetonitrile (125 mL) were stirred at room temperature for 24 hours. The reaction mixture was filtered to give 0.66 g (54%) of 3-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-benzonitrile as a pale yellow solid: mp 296-298°C (dec);  $^1$ H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.79 (br s, 1H), 7.94 (br s, 1H), 7.67 (d, 1H), 7.64 (dm, 1H), 7.53 (t, 1H), 7.45 (dm, 1H), 3.98 (m, 1H), 1.17 (d, 3H), 0.91 (s, 9H). IR (KBr): 3193, 3148, 2974, 2228, 1793, 1673, 1582, 1544 cm<sup>-1</sup>; MS (m/z) 297 (M<sup>+</sup>).

40

45

Elemental analysis for C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 68.67;	H, 6.44;	N, 14.13
Found	C, 68.73;	H, 6.36;	N, 14.04

50

N-(3-Cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide was prepared according to the procedure described in Example 9. From the product of the preceding paragraph (0.18 g, 0.61 mmol) and acetic anhydride (0.28 mL, 3.0 mmol) in pyridine (1.8 mL) there was obtained 0.14 g (68%) of white crystals: mp 253-254°C;  $^1$ H NMR (CDCl<sub>3</sub>):  $\delta$  7.81 (dt, 1H), 7.69-7.58 (m, 3H), 7.41 (br d, 1H), 4.27 (m, 1H), 2.01 (s, 3H), 1.25 (d, 3H), 0.99 (s, 9H). IR (KBr): 3337, 2965, 2237, 1804, 1739, 1684, 1619 cm<sup>-1</sup>; MS (m/z) 339 (M<sup>+</sup>).

55

Elemental analysis for C <sub>19</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 67.24;	H, 6.24;	N, 12.38
Found	C, 67.21;	H, 6.20;	N, 12.38

EXAMPLE 15(R)-N-(4-Cyano-phenyl)-N-[2-(1-cyclohexyl-ethylamino)-3,4-dioxo-cyclobut-1-enyl]-acetamide

(R)-4-[2-(1-Cyclohexyl-ethylamino)-3,4-dioxo-cyclobut-1-enylamino]-benzonitrile was prepared according to the procedure described in Example 10, first paragraph. From 4-(3,4-dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (0.36 g, 1.5 mmol) and (R)-(-)-1-cyclohexylethylamine (0.29 mL, 1.95 mmol) in absolute ethanol (5 mL) there was obtained after trituration with hot methanol 0.31 g (64%) of a yellow solid: mp 275-280°C (dec); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.87 (br s, 1H), 7.78 (d, 2H), 7.72 (d, 1H), 7.59 (d, 2H), 3.96 (m, 1H), 1.78-1.66 (m, 4H), 1.62 (m, 1H), 1.34 (m, 1H), 1.24-0.90 (m including a doublet at δ 1.20, 8H). IR (KBr): 3200, 2920, 2850, 2220, 1790, 1660, 1600, 1560, 1528 cm<sup>-1</sup>; MS (m/z) 323 (M<sup>+</sup>).

Elemental analysis for C <sub>19</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 70.57;	H, 6.55;	N, 12.99
Found	C, 70.19;	H, 6.60;	N, 13.00

15

This compound was prepared according to the procedure described in Example 12, second paragraph. From the product of the preceding paragraph (0.33 g, 1.02 mmol) and acetic anhydride (0.29 mL, 3.06 mmol) in pyridine (3.1 mL) there was obtained 0.62 g (40%) of (R)-N-(4-cyano-phenyl)-N-[2-(1-cyclohexylethylamino)-3,4-dioxo-cyclobut-1-enyl]-acetamide as a yellow solid: mp 194-198°C; [α]<sub>D</sub><sup>25</sup> = -150.96° (DMSO, c 0.0084); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.82 (d, 2H), 7.46 (d, 2H), 7.25 (br m, 1H), 4.28 (m, 1H), 2.02 (s, 3H), 1.87-0.94 (m including a doublet at δ 1.27, 14H). IR (KBr): 3337, 2930, 2865, 2237, 1803, 1729, 1690, 1620 cm<sup>-1</sup>; MS (m/z) 365 (M<sup>+</sup>).

25

Elemental analysis for C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 69.02;	H, 6.34;	N, 11.50
Found	C, 68.72;	H, 6.10;	N, 11.55

30

EXAMPLE 16N-(2-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(4-cyano-phenyl)-acetamide

4-[2-Butylamino-3,4-dioxo-cyclobut-1-enylamino]-benzonitrile was prepared according to the procedure described in Example 11, first paragraph. From 4-(3,4-dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (1 g, 4.1 mmol) and butylamine (3 g, 41.0 mmol) in acetonitrile (125 mL) there was obtained 0.64 g (58%) of a yellow solid: mp 256-258°C (dec); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.00 (br s, 1H), 7.81 (br s, 1H), 7.77 (d, 2H), 7.57 (d, 2H), 3.60 (br q, 2H), 1.55 (quintet, 2H), 1.34 (sextet, 2H), 0.90 (t, 3H). IR (KBr): 3240, 2980, 2240, 1800, 1670, 1625, cm<sup>-1</sup>; MS (m/z) 269 (M<sup>+</sup>).

40

Elemental analysis for C <sub>15</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 66.90;	H, 5.61;	N, 15.60
Found	C, 66.23;	H, 5.80;	N, 15.54

45

N-(2-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(4-cyano-phenyl)-acetamide was prepared according to the procedure described in Example 12, paragraph two. From the product of the preceding paragraph (0.16 g, 0.59 mmol) and acetic anhydride (0.28 mL, 2.96 mmol) in pyridine (1.8 mL) there was obtained 0.05 g (27%) of white solid: mp 194-196°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.82 (d, 2H), 7.45 (d, 2H), 7.34 (br m, 1H), 3.78 (q, 2H), 2.01 (s, 3H), 1.65 (quintet, 2H), 1.44 (sextet, 2H), 0.98 (t, 3H). IR (KBr): 3315, 2957, 2228, 1796, 1727, 1696, 1598 cm<sup>-1</sup>; MS (m/z) 311 (M<sup>+</sup>).

50

Elemental analysis for C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 65.58;	H, 5.50;	N, 13.50
Found	C, 65.45;	H, 5.63;	N, 13.45

55

**EXAMPLE 17****N-(endo)-[2-(Bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enyl]-N-(4-cyano-phenyl)-acetamide**

(endo)-4-[2-(Bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enylamino]-benzonitrile was prepared according to the procedure described in Example 11, first paragraph. From 4-(3,4-dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (0.37 g, 1.5 mmol) and ( $\pm$ )-endo-2-aminonorbornane (0.17 g, 1.5 mmol) in acetonitrile (30 mL) there was obtained after trituration with diethyl ether 0.32 g (69%) of a yellow solid: mp 251-252°C (dec);  $^1$ H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.88 (br s, 1H), 7.85 (d, 1H), 7.78 (d, 2H), 7.60 (d, 2H), 4.35 (m, 1H), 2.36 (m, 1H), 2.23 (m, 1H), 2.2 (m, 1H), 1.69-1.23 (m, 6H), 0.91 (m, 1H). IR (KBr): 3200, 2942, 2220, 1798, 1668, 1600, 1565, 1535 cm<sup>-1</sup>; MS (m/z) 307 (M<sup>+</sup>).

15

Elemental analysis for C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 70.34;	H, 5.57;	N, 13.67
Found	C, 70.03;	H, 5.38;	N, 13.97

20

N-(endo)-[2-(Bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enyl]-N-(4-cyano-phenyl)-acetamide was prepared according to the procedure described in Example 9. From the product of the preceding paragraph (0.021 g, 0.068 mmol) and acetic anhydride (0.033 mL, 0.35 mmol) in pyridine (0.21 mL) there was obtained 0.014 g (59%) of pale yellow solid: mp 282-285°C (dec);  $^1$ H NMR (CDCl<sub>3</sub>):  $\delta$  7.82 (d, 2H), 7.45 (d, 2H), 7.51 (br d, 1H), 4.63 (m, 1H), 2.48 (m, 1H), 2.31 (m, 1H), 2.20 (m, 1H), 2.02 (s, 3H), 1.75-1.30 (m, 6H), 0.96 (m, 1H). IR (KBr): 3343, 2957, 2239, 1803, 1730, 1690, 1620 cm<sup>-1</sup>; MS (m/z) 349 (M<sup>+</sup>).

25

Elemental analysis for C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 68.75;	H, 5.48;	N, 12.03
Found	C, 68.39;	H, 5.39;	N, 12.02

**EXAMPLE 18**

30

**N-(2-tert-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(isoquinolin-5-yl)-acetamide**

35

5-Aminoisoquinoline (4.24 g, 29.4 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (5 g, 29.4 mmol) in absolute ethanol (100 mL) were refluxed overnight. The reaction mixture was filtered to give 2.3 g of a solid which was used without further purification. This solid (0.3 g, 1.12 mmol) in *tert*-butylamine (50 mL) was refluxed for 3 hours. The reaction mixture was concentrated and triturated with diethyl ether to give 0.12 g (39%) of 3-tert-Butylamino-4-(isoquinolin-5-ylamino)-cyclobut-3-ene-1,2-dione as a white solid 0.125 hydrate: mp 268-270°C (dec);  $^1$ H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.75 (s, 1H), 9.35 (s, 1H), 8.62 (d, 1H), 8.19 (s, 1H), 8.01 (d, 1H), 7.88 (d, 1H), 7.80 (d, 1H), 7.68 (t, 1H), 1.47 (s, 9H). IR (KBr): 3200, 1785, 1670, 1600 cm<sup>-1</sup>; MS (m/z) 295 (M<sup>+</sup>).

40

Elemental analysis for C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> · 0.125 H <sub>2</sub> O			
Calc'd	C, 69.14;	H, 5.80;	N, 14.23
Found	C, 68.08;	H, 5.78;	N, 13.75

45

50

N-(2-tert-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(isoquinolin-5-yl)-acetamide was prepared according to the procedure described in Example 12, second paragraph. From the product of the preceding paragraph (0.30 g, 1.0 mmol) and acetic anhydride (0.29 mL, 3.0 mmol) in pyridine (3 mL) there was obtained 0.18 g (53%) of off-white crystals: mp 210-213°C;  $^1$ H NMR (CDCl<sub>3</sub>):  $\delta$  9.41 (s, 1H), 8.66 (d, 1H), 8.19 (m, 1H), 8.09 (br s, 1H), 7.81-7.72 (m, 2H), 7.59 (d, 1H), 1.89 (s, 3H), 1.56 (s, 9H). IR (KBr): 3304, 2965, 1793, 1679, 1588 cm<sup>-1</sup>; MS (m/z) 337 (M<sup>+</sup>).

55

Elemental analysis for C <sub>19</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 67.64;	H, 5.68;	N, 12.46
Found	C, 67.38;	H, 5.65;	N, 12.41

**EXAMPLE 19****N-(2-tert-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(pyridin-3-yl)-acetamide**

5        3-Aminopyridine (2.77 g, 29.4 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (5 g, 29.4 mmol) in absolute ethanol (150 mL) were refluxed for 18 hours. The reaction mixture was concentrated and chromatographed in hexanes/ethyl acetate (1/4) to give 3.15 g of a white solid. This solid (2.6 g, 11.9 mmol) in tert-butylamine (50 mL) was refluxed for 3 hours. The reaction mixture was concentrated and triturated with diethyl ether to give 1.05 g (36%) of 3-tert-butylamino-4-(pyridin-3-ylamino)-cyclobut-3-ene-1,2-dione as a white solid: mp 250-252°C (dec); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.57 (s, 1H), 8.23 (d, 1H), 7.96 (d, 1H), 7.37 (m, 1H), 1.43 (s, 9H). IR (KBr): 1790, 1685, 1600 cm<sup>-1</sup>; MS (m/z) 245 (M<sup>+</sup>).

15        Elemental analysis for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>

Calc'd	C, 63.66; H, 6.16; N, 17.13
Found	C, 63.28; H, 6.22; N, 17.07

20        N-(2-tert-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(pyridin-3-yl)-acetamide was prepared according to the procedure described in Example 12, second paragraph. From the product of the preceding paragraph (0.20 g, 0.82 mmol) and acetic anhydride (0.23 mL, 2.5 mmol) in pyridine (2.5 mL) there was obtained 0.15 g (68%) of white crystals: mp 194-195°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.74 (d, 1H), 8.62 (s, 1H), 7.83 (br s, 1H), 7.70 (m, 1H), 7.47 (dd, 1H), 2.00 (s, 3H), 1.52 (s, 9H). IR (KBr): 3435, 3298, 1799, 1741, 1685, 1598 cm<sup>-1</sup>; MS (m/z) 288 ([M+H]<sup>+</sup>).

25        Elemental analysis for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>

Calc'd	C, 62.71; H, 5.96; N, 14.62
Found	C, 62.78; H, 5.91; N, 14.67

**EXAMPLE 20****N-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-N-(2-methoxy-5-trifluoromethyl-phenyl)-acetamide**

35        2-Methoxy-5-trifluoromethylaniline (5.62 g, 29.4 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (5 g, 29.4 mmol) in absolute ethanol (100 mL) were refluxed for 66 hours. The reaction mixture was filtered and the precipitate was chromatographed in methanol/methylene chloride to give 1.88 g of a yellow solid. This solid (1.0 g, 3.2 mmol) and 2-amino-3,3-dimethylbutane (0.43 mL, 3.2 mmol) in absolute ethanol (20 mL) were stirred at room temperature for 18 hours. The reaction mixture was concentrated and chromatographed with methylene chloride/methanol (96:4) to give 0.91 g (78%) of 3-ethoxy-4-(2-methoxy-5-trifluoromethyl-phenylamino)-cyclobut-3-ene-1,2-dione as a white solid: mp 143-155°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.36 (s, 1H), 8.24 (d, 1H), 8.19 (d, 1H), 7.35 (dd, 1H), 3.99 (s, 3H), 1.18 (d, 3H), 0.91 (s, 9H). IR (KBr): 3293, 2976, 1802, 1690, 1591, 1543 cm<sup>-1</sup>; MS (m/z) 370 (M<sup>+</sup>).

45        Elemental analysis for C<sub>18</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>

Calc'd	C, 58.37; H, 5.72; N, 7.56
Found	C, 57.98; H, 5.65; N, 7.27

50        N-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-N-(2-methoxy-5-trifluoromethyl-phenyl)-acetamide was prepared according to the procedure described in Example 12, second paragraph. From the product of the preceding paragraph (0.20 g, 0.54 mmol) and acetic anhydride (0.15 mL, 1.6 mmol) in pyridine (1.6 mL) there was obtained 0.16 g (73%) of white crystals: mp 76-79°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.73 (dd, 1H), 7.53 (d, 1H), 7.38 (br d, 1H), 7.12 (d, 1H), 4.25 (m, 1H), 3.92 (s, 3H), 1.96 (s, 3H), 1.24 (d, 3H), 1.00 and 0.99 (two singlets, 9H). IR (KBr): 3326, 2974, 1799, 1715, 1609 cm<sup>-1</sup>; MS (m/z) 412 (M<sup>+</sup>).

55        Elemental analysis for C<sub>20</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>

Calc'd	C, 58.25; H, 5.62; N, 6.79
Found	C, 58.44; H, 5.85; N, 6.47

EXAMPLE 21(endo)-N-[2-(Bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enyl]-N-(pyridin-4-yl)-acetamide

5 4-Aminopyridine (2.77 g, 29.4 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (5 g, 29.4 mmol) in absolute ethanol (100 mL) were refluxed for 4 hours. The reaction mixture was concentrated and chromatographed in ethyl acetate to give 0.63 g of a white solid. This solid (0.33 g, 1.5 mmol) and (+)-(endo)-2-aminonorbornane (0.17 g, 1.5 mmol) in acetonitrile (30 mL) was stirred at room temperature for 24 hours. The reaction mixture was filtered and triturated with diethyl ether to give 0.35 g (36%) of ( $\pm$ )-(endo)-3-(bicyclo[2.2.1]hept-2-ylamino)-4-(pyridin-4-ylamino)-cyclobut-3-ene-10 1,2-dione as a pale yellow solid 1.56 hydrate: mp 270-277°C (dec);  $^1$ H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.81 (br s, 1H), 8.41 (d, 2H), 7.88 (d, 1H), 7.44 (d, 2H), 4.34 (m, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 2.10 (m, 1H), 1.69-1.20 (m, 6H), 0.90 (m, 1H). IR (KBr): 3365, 2957, 1799, 1691, 1630, 1599, 1533 cm<sup>-1</sup>; MS (m/z) 283 (M<sup>+</sup>).

15

Elemental analysis for C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> · 1.56 H <sub>2</sub> O			
Calc'd	C, 61.71;	H, 6.51;	N, 13.49
Found	C, 61.76;	H, 6.37	N, 13.27

20

(endo)-N-[2-(Bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enyl]-N-(pyridin-4-yl)-acetamide was prepared according to the procedure described in Example 12, second paragraph. From the product of the preceding paragraph (0.17 g, 0.60 mmol) and acetic anhydride (0.28 mL, 3.0 mmol) in pyridine (1.8 mL) there was obtained 0.08 g (41%) of pale yellow solid: mp 192-194°C;  $^1$ H NMR (CDCl<sub>3</sub>):  $\delta$  8.80 (dd, 2H), 7.49 (br d, 1H), 7.30 (dd, 2H), 4.63 (m, 1H), 2.48 (m, 1H), 2.30 (m, 1H), 2.19 (m, 1H), 2.06 (s, 3H), 1.75-1.30 (m, 6H), 0.97 (m, 1H). IR (KBr): 3348, 2954, 1799, 1735, 1696, 1621 cm<sup>-1</sup>; MS (m/z) 325 ([M+H]<sup>+</sup>).

25

Elemental analysis for C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 66.45;	H, 5.89;	N, 12.91
Found	C, 66.02;	H, 5.87;	N, 12.66

30

EXAMPLE 22N-(2-sec-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(4-cyano-phenyl)-acetamide

35

4-[2-sec-Butylamino-3,4-dioxo-cyclobut-1-enylamino]-benzonitrile was prepared according to the procedure described in Example 11, first paragraph. From 4-(3,4-dioxo-2-ethoxy-cyclobut-1-enylamino)-benzonitrile (1 g, 4.1 mmol) and ( $\pm$ )-sec-butylamine (excess) in acetonitrile (125 mL) there was obtained 1.36 g of a yellow solid: mp 245-247°C;  $^1$ H NMR (DMSO-d<sub>6</sub>):  $\delta$  9.89 (br s, 1H), 7.78 (d, 2H), 7.73 (d, 1H), 7.58 (d, 2H), 4.01 (m, 1H), 1.65-1.46 (m 2H), 1.23 (d, 3H), 0.89 (t, 3H). IR (KBr): 3217, 3185, 3000, 2228, 1798, 1664, 1609, 1527 cm<sup>-1</sup>; MS (m/z) 269 (M<sup>+</sup>).

40

Elemental analysis for C <sub>15</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 66.90;	H, 5.61;	N, 15.60
Found	C, 66.78;	H, 5.43;	N, 15.61

45

N-(2-sec-Butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(4-cyano-phenyl)-acetamide was prepared according to the procedure described in Example 12, second paragraph. From the product of the preceding paragraph (0.16 g, 0.52 mmol) and acetic anhydride (0.28 mL, 2.96 mmol) in pyridine (1.8 mL) there was obtained 0.14 g (78%) of yellow crystals: mp 220-225°C (dec.);  $^1$ H NMR (CDCl<sub>3</sub>):  $\delta$  7.80 (d, 2H), 7.44 (d, 2H), 7.14 (br d, 1H), 4.36 (m, 1H), 2.00 (s, 3H), 1.71-1.53 (m, 2H), 1.30 (d, 3H), 0.98 (s, 3H). IR (KBr): 3348, 2978, 2239, 1803, 1739, 1690, 1622 cm<sup>-1</sup>; MS (m/z) 311 (M<sup>+</sup>).

50

Elemental analysis for C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 65.58;	H, 5.50;	N, 13.50
Found	C, 65.18;	H, 5.31;	N, 13.33

**EXAMPLE 23****(R)-N-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-N-(pyridin-3-yl)-acetamide**

5 3-Aminopyridine (2.77 g, 29.4 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (5 g, 29.4 mmol) in acetonitrile (35 mL) were refluxed for 18 hours. The reaction mixture was concentrated and chromatographed with 2% methanol in ethyl acetate to give 2.65 g of a white solid. This solid (0.9 g, 4.1 mmol) was stirred in a solution of (R)-1,2,2-trimethyl-propylamine (8.2 mmol) and ethanol (50 mL) at room temperature for 24 hours. The reaction mixture was filtered and rinsed with ethyl acetate to give 0.77 g (68%) of (+)-(R)-3-(1,2,2-trimethyl-propylamino)-4-(pyridin-3-ylamino)-cyclobut-10 3-ene-1,2-dione as a white solid: mp 283-285°C;  $[\alpha]_D^{25} = +2.04^\circ$  (DMSO, c 0.0098);  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>):  $\delta$  8.19 (brs, 1H), 8.57 (d, 1H), 8.22 (dd, 1H), 7.96 (dm, 1H), 7.66 (brd, 1H), 7.37 (dd, 1H), 3.98 (m, 1H), 1.17 (d, 3H), 0.91 (s, 9H). IR (KBr): 3200, 2960, 1790, 1655, 1570, 1455 cm<sup>-1</sup>; MS (m/z) 273 (M<sup>+</sup>).

Elemental analysis for C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 65.91;	H, 7.01;	N, 15.37
Found	C, 65.88;	H, 7.04;	N, 15.56

15 The title compound was prepared according to the procedure described in Example 9. From the product of the preceding paragraph (0.20 g, 0.73 mmol) and acetic anhydride (0.21 mL, 2.2 mmol) in pyridine (2.2 mL) there was obtained 0.14 g (61%) of a 0.4 hydrate of the title compound as white crystals: mp 149-151°C;  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta$  8.75 (dd, 1H), 8.63 (d, 1H), 7.71 (dm, 1H), 7.49 (dd, 1H), 7.42 (brd, 1H), 2.27 (m, 1H), 2.01 (s, 3H), 1.26 (d, 3H), 1.00 (s, 9H). IR (KBr): 3325, 2960, 1800, 1740, 1690, 1620 cm<sup>-1</sup>; MS (m/z) 315 ([M+H]<sup>+</sup>).

Elemental analysis for C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> ·0.4 H <sub>2</sub> O			
Calc'd	C, 63.30;	H, 6.81;	N, 13.03
Found	C, 63.45;	H, 6.71;	N, 12.98

**EXAMPLE 24****(R)-N-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-N-(pyridin-4-yl)-acetamide**

35 4-Aminopyridine (8.27 g, 87.9 mmol) and 3,4-diethoxy-3-cyclobutene-1,2-dione (15 g, 88 mmol) in acetonitrile (51 mL) were refluxed for 18 hours. The reaction mixture was diluted with ethanol, filtered and concentrated. Chromatography with 2% methanol in ethyl acetate afforded 2.59 g of a white solid. This solid (0.9 g, 4.1 mmol) was stirred in a solution of (R)-1,2,2-trimethyl-propylamine (8.2 mmol) and ethanol (50 mL) at room temperature for 24 hours. The reaction mixture was filtered and rinsed with ethyl acetate to give 0.70 g (62%) of (+)-(R)-3-(1,2,2-trimethyl-propylamino)-4-(pyridin-4-ylamino)-cyclobut-1,2-dione as a white solid: mp 275-279°C (dec);  $[\alpha]_D^{25} = +6.02^\circ$  (DMSO, c 0.0066);  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>):  $\delta$  9.80 (s, 1H), 8.41 (dd, 2H), 7.73 (brd, 1H), 7.45 (dd, 2H), 3.97 (m, 1H), 1.17 (d, 3H), 0.91 (s, 9H). IR (KBr): 3210, 3160, 1800, 1670, 1610, 1530 cm<sup>-1</sup>; MS (m/z) 273 (M<sup>+</sup>).

Elemental analysis for C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>			
Calc'd	C, 65.91;	H, 7.01;	N, 15.37
Found	C, 65.80;	H, 7.01;	N, 15.60

50 The title compound was prepared according to the procedure described in Example 9. From the product of the preceding paragraph (0.20 g, 0.73 mmol) and acetic anhydride (0.21 mL, 2.2 mmol) in pyridine (2.2 mL) there was obtained 0.08 g (35%) of the title compound as a white solid: mp 140-142°C (dec);  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta$  8.81 (dd, 2H), 7.32 (brd, 1H), 7.28 (dd, 2H), 4.27 (m, 1H), 2.05 (s, 3H), 1.25 (d, 3H), 0.99 (s, 9H). IR (KBr): 3340, 2980, 1790, 1720, 1690, 1610 cm<sup>-1</sup>; MS (m/z) 315 ([M+H]<sup>+</sup>).

Elemental analysis for C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 64.74;	H, 6.71;	N, 13.32
Found	C, 64.46;	H, 6.68;	N, 13.13

EXAMPLE 25(R)-N-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-3-methyl-N-(pyridin-4-yl)-butyramide

5 This compound was prepared according to the procedure described in Example 9. From the product of the first paragraph of Example 24 (0.17 g, 0.62 mmol) and isovaleric anhydride (0.36 mL, 1.86 mmol) in pyridine (2.5 mL) there was obtained 0.08 g (36%) of the title compound as an off-white solid: mp 193-196°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.81 (dd, 2H), 7.36 (dm, 1H), 7.27 (dd, 2H), 4.28 (m, 1H), 2.20-2.02 (m, 3H), 1.26 (d, 3H), 0.99 (s, 9H), 0.90 (d, 3H), 0.89 (d, 3H). IR (KBr): 3310, 2950, 1795, 1720, 1700, 1610 cm<sup>-1</sup>; MS (m/z) 357 ([M+H]<sup>+</sup>).

10

Elemental analysis for C <sub>20</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>		
Calc'd	C, 67.20; H, 7.61; N, 11.76	
Found	C, 66.71; H, 7.63; N, 11.63	

15

EXAMPLE 26(R)-(-)-N-(3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl)-N-(pyridin-4-yl)-pentylamide

20 This compound was prepared according to the procedure described in Example 9. From the product of the first paragraph of Example 24 (0.20 g, 0.73 mmol) and valeric anhydride (0.42 mL, 2.2 mmol) in pyridine (2.9 mL) there was obtained 0.17 g (65%) of the title compound as a pale yellow solid: mp 160-165°C (dec); [α]<sub>D</sub><sup>25</sup> = -202.72° (DMSO, c 0.0076); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.81 (dd, 2H), 7.38 (dm, 1H), 7.28 (dd, 2H), 4.28 (m, 1H), 2.18 (dt, 2H), 1.59 (m, 2H), 1.31-1.20 (m, 2H), 1.26 (d, 3H), 1.00 (s, 9H), 0.85 (t, 3H). IR (KBr): 3310, 2970, 1795, 1720, 1700, 1610 cm<sup>-1</sup>; MS (m/z) 357 ([M+H]<sup>+</sup>).

25

Elemental analysis for C <sub>20</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>		
Calc'd	C, 67.20; H, 7.61; N, 11.76	
Found	C, 66.93; H, 7.73; N, 11.84	

30

EXAMPLE 27(R)-(-)-N-(4-Cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-butyramide

35

3,4-Diethoxy-3-cyclobutene-1,2-dione (0.5 g, 2.9 mmol) was added to the reaction mixture and the temperature of the oil bath increased to 150°C. After 48 hours the reaction mixture was cooled to room temperature, then diluted with ethyl acetate and filtered. The filtrate was concentrated and the resulting solid was taken up in ethyl acetate (5 mL) and sonicated. Filtration gave 0.54 g (34%) of 4-(3,4-dioxo-2-ethoxy-cyclobut-1-enylamino)-3-ethylbenzonitrile as a light brown solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.56 (br s, 1H), 7.70 (br s overlapping a doublet at δ 7.69, 2H), 7.30 (d, 1H), 4.71 (q, 2H), 2.74 (q, 2H), 1.37 (t, 3H), 1.15 (t, 3H).

40

4-(2-ethoxy-3,4-dioxo-cyclobut-1-enylamino)-3-ethylbenzonitrile (1.26 g, 4.66 mmol) and a solution of (R)-1,2,2-trimethylpropylamine (9.3 mmol) in ethanol (58 mL) were stirred at room temperature for 24 hours. The resulting yellow solution was concentrated to a yellow oil, which was dissolved in acetonitrile (20 mL) and stirred at room temperature. The yellow solid which precipitated was filtered off and rinsed with ethyl acetate to yield 0.79 g (52%) of (+)-(R)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethylbenzonitrile as an off-white solid: mp 235-237°C; [α]<sub>D</sub><sup>25</sup> = +68.20° (DMSO, c 0.0072); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.04 (br s, 1H), 8.04 (d, 1H), 7.69-7.57 (m, 3H), 4.05 (m, 1H), 2.71 (q, 2H), 1.27-1.16 (overlapping doublet and triplet, 6H), 0.91 (s, 9H). IR (KBr): 3278, 2959, 2222, 1793, 1674, 1598, 1576, 1522 cm<sup>-1</sup>; MS (m/z) 325 (M<sup>+</sup>).

50

Elemental analysis for C <sub>19</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>		
Calc'd	C, 70.13; H, 7.12; N, 12.91	
Found	C, 69.82; H, 7.17; N, 12.99	

55

A mixture of the product of the preceding paragraph (0.37 g, 1.14 g), butyric anhydride (0.47 mL, 2.87 mmol) and pyridine (10 mL) was stirred at rt overnight. The solution was stripped free of solvent and the resulting oil was taken

up in hexanes. The precipitate which formed was filtered off and recrystallized (EtOAc/hexanes) to afford the title compound as 0.26 g (58%) of a white solid: mp 150-152°C;  $[\alpha]^{25}_D$  -193.90° (DMSO, c 0.0098);  $^1H$  NMR (DMSO-d<sub>6</sub>): δ 7.93 (d, 1H), 7.82 (d, 1H), 7.80-7.50 (m, 2H), 4.10 (m, 1H), 2.53 (m, 2H), 2.18 (m, 1H), 1.97 (m, 1H), 1.53 (m, 2H), 1.20 (m, 3H), 1.14 (m, 3H), 0.93 (s, 9H), 0.80 (t, 3H). IR (KBr): 3340, 2980, 2230, 1800, 1730, 1690, 1600 cm<sup>-1</sup>; MS (m/z) 395 (M<sup>+</sup>).

Elemental analysis for C <sub>23</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 69.85;	H, 7.39;	N, 10.62
Found	C, 69.70;	H, 7.46;	N, 10.60

### EXAMPLE 28

#### (R)-N-(4-Cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-propionamide

(+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethylbenzonitrile (0.40 g, 1.23 mmol), propionic anhydride (0.47 mL, 3.67 mmol) and pyridine (3.7 mL) were mixed and allowed to stand at room temperature for 24 hours. The reaction mixture was filtered to remove undissolved solid material and the filtercake was rinsed with dichloromethane. The combined filtrate was concentrated and the resulting yellow gum was crystallized with hexanes (20 mL). Solvent was decanted off and the solid material was triturated with hexanes to afford the title compound as 0.45 g (96%) of an off-white solid:  $^1H$  NMR (CDCl<sub>3</sub>): δ 7.70 (s, 1H), 7.62 (m, 1H), 7.52 (m, 1H), 7.37 (m, 1H), 4.28 (m, 1H), 2.70-2.50 (m, 2H), 2.20-2.09 (m, 1H), 2.03-1.92 (m, 1H), 1.30-1.24 (m, 6H), 1.09 (t, 3H), 1.00 (d, 9H). IR (KBr): 3330, 2970, 2230, 1800, 1730, 1680, 1610 cm<sup>-1</sup>; MS (m/z) 381 (M<sup>+</sup>).

Elemental analysis for C <sub>22</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 69.27;	H, 7.13;	N, 11.02
Found	C, 69.25;	H, 7.30;	N, 10.96

### EXAMPLE 29

#### (R)-(-)-N-(4-Cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-crotonamide

(+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethylbenzonitrile (0.40 g, 1.23 mmol), crotonic anhydride (0.55 mL, 3.71 mmol) and pyridine (3.7 mL) were mixed and allowed to stand at room temperature for 24 hours. The reaction mixture was filtered to remove undissolved solid material and the filtercake was rinsed with dichloromethane. The combined filtrate was concentrated and the resulting red-brown solid was triturated with hexanes to afford the title compound as 0.48 g (99%) of an off-white solid:  $[\alpha]^{25}_D$  -245.1° (DMSO, c 0.011);  $^1H$  NMR (CDCl<sub>3</sub>): δ 7.70 (s, 1H), 7.68-7.55 (m, 2H), 7.34 (m, 1H), 7.22 (m, 1H), 5.54 (m, 1H), 4.28 (m, 1H), 2.67-2.48 (m, 2H), 1.84 (m, 3H), 1.27 (m, 3H), 1.24 (t, 3H), 1.00 (d, 9H). IR (KBr): 3450, 3300, 2980, 2230, 1790, 1725, 1675, 1625 cm<sup>-1</sup>; MS (m/z) 393 (M<sup>+</sup>).

Elemental analysis for C <sub>23</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub>			
Calc'd	C, 70.21;	H, 6.92;	N, 10.68
Found	C, 69.91;	H, 7.04;	N, 10.49

### EXAMPLE 30

#### (R)-(-)-N-(4-Cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide

(+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethylbenzonitrile (0.36 g, 1.11 mmol), acetic anhydride (0.31 mL, 3.29 mmol) and pyridine (3.4 mL) were mixed and allowed to stand at room temperature for 24 hours. The reaction mixture was filtered to remove undissolved solid material and the filtercake was rinsed with ethyl acetate. The combined filtrate was concentrated and the resulting solid was purified by recrystallization (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) and trituration (EtOAc) to afford the title compound as 0.29 g (71%) of a white solid: mp 229-231°C;  $[\alpha]^{25}_D$  -224.43° (DMSO, c 0.0092);  $^1H$  NMR (CDCl<sub>3</sub>): δ 7.72 (s, 1H), 7.64 (m, 1H), 7.54-7.40 (m, 1H), 7.38 (m, 1H), 4.37 (m, 1H), 2.72-2.53 (m, 2H), 1.92 (s, 3H), 1.32-1.23 (m, 6H), 0.99 (d, 9H). IR (KBr): 3450, 3340, 2970, 2240, 1800,

1725, 1680, 1610  $\text{cm}^{-1}$ ; MS (m/z) 367 (M $^+$ ).

Elemental analysis for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3$			
Calc'd	C, 68.64;	H, 6.86;	N, 11.43
Found	C, 68.31;	H, 6.82;	N, 11.25

### EXAMPLE 31

**(R)-(-)-N-(4-Cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-pentanamide**

(+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethylbenzonitrile (0.40 g, 1.23 mmol), valeric anhydride (0.73 mL, 3.62 mmol) and pyridine (3.7 mL) were mixed and allowed to stand at room temperature for 24 hours. The reaction mixture was filtered to remove undissolved solid material and the filtercake was rinsed with dichloromethane. The combined filtrate was concentrated and the resulting yellow gum was crystallized with hexanes (20 mL). Solvent was decanted off and the solid was triturated with hexanes to afford the title compound as 0.47 g (93%) of an off-white solid:  $[\alpha]^{25}_D$  -199.0° (DMSO, c 0.0098);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.71 (s, 1H), 7.63 (d, 1H), 7.58-7.42 (m, 1H), 7.37 (t, 1H), 4.28 (m, 1H), 2.69-2.50 (m, 2H), 2.17-2.05 (m, 1H), 2.01-1.90 (m, 1H), 1.57 (m, 2H), 1.30-1.20 (m, 8H), 0.99 (d, 9H), 0.85 (t, 3H). IR (KBr): 3430, 3330, 2970, 2240, 1800, 1730, 1690, 1610  $\text{cm}^{-1}$ ; MS (m/z) 409 (M $^+$ ).

Elemental analysis for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_3$			
Calc'd	C, 70.39;	H, 7.63;	N, 10.26
Found	C, 70.31;	H, 7.80;	N, 10.20

### EXAMPLE 32

**(R)-(-)-N-(4-cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-cyclohexanecarboxamide**

(+)-(R)-4-[3,4-Dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethylbenzonitrile (0.50 g, 1.54 g), cyclohexanecarboxylic acid anhydride (0.92 g, 3.86 mmol) and pyridine (15 mL) were combined and stirred at room temperature for 2 days. The mixture was filtered and stripped free of solvent. The resulting oil was crystallized with diethyl ether/hexanes and the solid which formed was filtered off and recrystallized (EtOAc/hexanes) to afford the title compound as 0.39 g (58%) of a white solid: mp 156-159°C;  $[\alpha]^{25}_D$  -226.61° (DMSO, c 0.0096);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.72 (s, 1H), 7.62 (d, 1H), 7.57-7.40 (m, 1H), 7.38 (m, 1H), 4.28 (m, 1H), 2.69-2.48 (m, 2H), 2.04-1.94 (m, 1H), 1.78-1.65 (m, 3H), 1.65-1.57 (m, 3H), 1.50-1.48 (m, 1H), 1.30-1.23 (m, 6H), 1.23-1.12 (m, 1H), 1.07-0.87 (m, 2H), 0.99 (d, 9H). IR (KBr): 3430, 3340, 2940, 2230, 1800, 1730, 1690, 1610  $\text{cm}^{-1}$ ; MS (m/z) 435 (M $^+$ ).

Elemental analysis for $\text{C}_{16}\text{H}_{33}\text{N}_3\text{O}_3$			
Calc'd	C, 71.70;	H, 7.64;	N, 9.65
Found	C, 71.88;	H, 7.64;	N, 9.61

### EXAMPLE 33

**(R)-(-)-N-(3-Chloro-4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide**

4-Amino-2-chlorobenzonitrile (3.14 g, 20.6 mmol) was added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (3.5 g, 20.6 mmol) in absolute ethanol (41 mL). The mixture was heated at reflux overnight and the resulting suspension filtered hot. The filtrate was concentrated to afford a yellow solid which was suspended in ethyl acetate, filtered, and washed several times with ethyl acetate to give 1.16 g of a yellow solid. This solid (0.5 g, 1.8 mmol) was stirred in a solution of (R)-1,2,2-trimethyl-propylamine (3.6 mmol) and ethanol (18 mL) at room temperature for 24 hours. The reaction mixture was filtered and rinsed with ethyl acetate to give 0.53 g (88%) of (R)-(+)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-2-chlorobenzonitrile a yellow solid: mp >300°C;  $[\alpha]^{25}_D$  = +1.87° (DMSO, c 0.010);  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.04 (brs, 1H), 7.91 (d, 1H), 7.87 (d, 1H), 7.76 (brd, 1H), 7.40 (dd, 1H), 3.98 (m, 1H),

1.18 (d, 3H), 0.91 (s, 9H). IR (KBr): 3200, 2970, 2230, 1800, 1675, 1575  $\text{cm}^{-1}$ ; MS (m/z) 331 ( $\text{M}^+$ ).

Elemental analysis for $\text{C}_{17}\text{H}_{18}\text{ClN}_3\text{O}_2$			
Calc'd	C, 61.54;	H, 5.47;	N, 12.66
Found	C, 61.29;	H, 5.46;	N, 12.45

5

This compound was prepared according to the procedure described in Example 12, second paragraph. From the product of the preceding paragraph (0.27 g, 0.81 mmol) and acetic anhydride (0.23 mL, 2.4 mmol) in pyridine (2.5 mL) there was obtained 0.16 g (53%) of the title compound as a white solid: mp 232-235°C (dec);  $[\alpha]_D^{25} = 307.5^\circ$  (DMSO, c 0.010);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.82 (d, 1H), 7.53 (d, 1H), 7.38 (dd, 1H), 7.34 (brd, 1H), 4.26 (m, 1H), 2.05 (s, 3H), 1.25 (d, 3H), 0.99 (s, 9H). IR (KBr): 3330, 2980, 2220, 1795, 1745, 1625  $\text{cm}^{-1}$ ; MS (m/z) 374 ( $[\text{M}+\text{H}]^+$ ).

10

15

Elemental analysis for $\text{C}_{19}\text{H}_{20}\text{ClN}_3\text{O}_3$			
Calc'd	C, 61.04;	H, 5.39;	N, 11.24
Found	C, 60.83;	H, 5.31;	N, 11.10

20

The smooth muscle relaxing activity of the compounds of this invention was established in accordance with standard pharmaceutically accepted test procedures with representative compounds as follows:

Sprague-Dawley rats (150-200 g) are rendered unconscious by  $\text{CO}_2$  asphyxiation and then euthanized by cervical dislocation. The bladder is removed into warm (37 deg.C) physiological salt solution (PSS) of the following composition (mM):  $\text{NaCl}$ , 118.4;  $\text{KCl}$ , 4.7;  $\text{CaCl}_2$ , 2.5;  $\text{MgSO}_4$ , 4.7;  $\text{H}_2\text{O}$ , 1.2;  $\text{NaHCO}_3$ , 24.9;  $\text{KH}_2\text{PO}_4$ , 1.2; glucose, 11.1; EDTA, 0.023; gassed with 95%  $\text{O}_2$ ; 2/5%  $\text{CO}_2$ ; pH 7.4. The bladder is opened and then cut into strips 1-2 mm in width and 7-10 mm in length. The strips are subsequently suspended in a 10 mL tissue bath under an initial resting tension of 1.5 g. The strips are held in place by two surgical clips one of which is attached to a fixed hook while the other is attached to an isometric force transducer. The preparations, which usually exhibit small spontaneous contractions, are allowed to recover for a period of 1 hour prior to a challenge with 0.1  $\mu\text{M}$  carbachol. The carbachol is then washed out and the tissue allowed to relax to its resting level of activity. Following a further 30 min period of recovery an additional 15 mM KCl are introduced into the tissue bath. This increase in KCl concentration results in a large increase in the amplitude of spontaneous contractions (and initiation of contractions in previously quiescent strips) superimposed upon a small increase in basal tone. Following stabilization of this enhanced level of contractile activity, incremental increases in the concentration of test compound or vehicle are introduced into the tissue bath. Contractile activity is measured for each compound or vehicle concentration during the last minute of a 30 minute challenge.

25

The isometric force developed by the bladder strips is measured using a concentration required to elicit 50% inhibition of pre-drug contractile activity ( $\text{IC}_{50}$  concentration) is calculated from this concentration-response curve. The maximum percentage inhibition of contractile activity evoked by a test compound is also recorded for concentrations of test compound less than or equal to 30  $\mu\text{M}$ .

30

The results of this study are shown in Table I.

35

Table I

Inhibition of Contractions in Isolated Rat Bladder Strips		
Compound	n	$\text{IC}_{50}$ $\mu\text{M}$
Example 1	2	0.50 $\pm$ 0.0
Example 2	2	0.29 $\pm$ 0.04
Example 5	2	0.35 $\pm$ 0.1
Example 6	4	0.57 $\pm$ 0.2
Example 7	2	0.37 $\pm$ 0.08
Example 9	4	0.23 $\pm$ 0.05
Example 10	2	0.31 $\pm$ 0.05
Example 11	2	9.7 $\pm$ 4.1
Example 13	2	0.2 $\pm$ 0.1
Example 14	2	3.2 $\pm$ 0.92
Example 16	2	1.24 $\pm$ 0.54
Example 17	2	1.84 $\pm$ 0.36

45

50

55

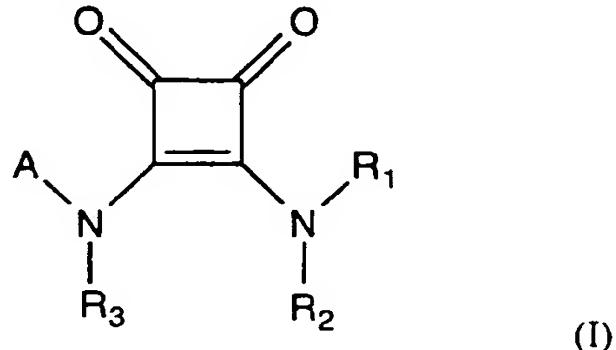
Table I (continued)

Inhibition of Contractions in Isolated Rat Bladder Strips		
Compound	n	IC <sub>50</sub> $\mu$ M
Example 21	1	10.6
Example 23	3	7.2±1.6
Example 24	2	2.5±0.2
Example 25	3	10.8±1.6
Example 26	4	4.9±1.2
Example 27	2	0.17±0.004
Example 28	4	0.22±0.2
Example 29	2	0.27±0.02
Example 30	4	0.35±0.1
Example 31	3	0.61±0.2
Example 32	2	0.63±0.065
Example 33	2	0.19±0.01

Hence, the compounds of this invention have a pronounced effect on smooth muscle contractility and are useful in the treatment of urinary incontinence, irritable bladder and bowel disease, asthma, hypertension, stroke, and similar diseases as mentioned above, which are amenable to treatment with potassium channel activating compounds by administration, orally, parenterally, or by aspiration to a patient in need thereof.

## Claims

1. A compound of the formula:

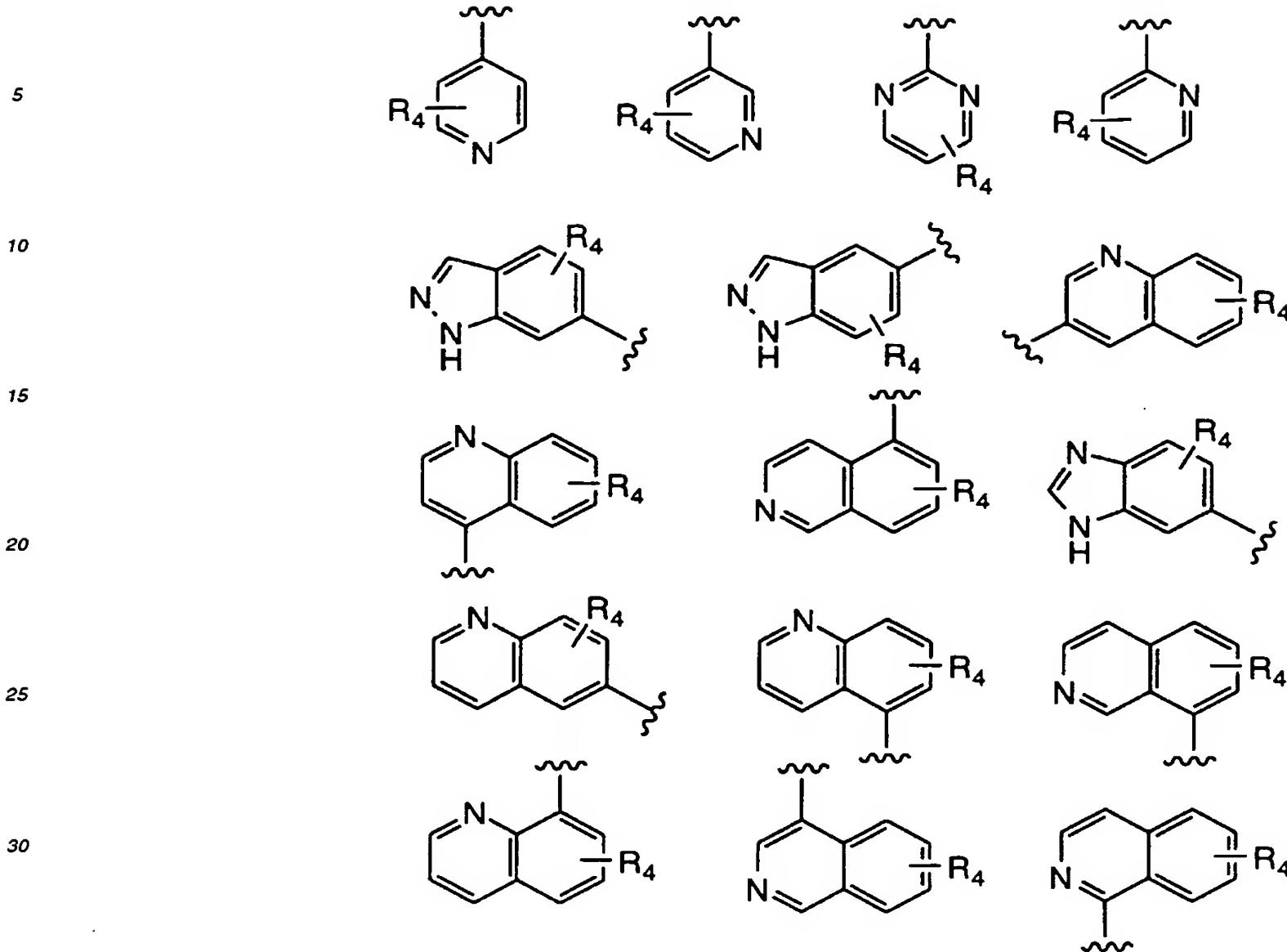


wherein:

45      R<sub>1</sub> and R<sub>2</sub> are, independent from each other, hydrogen, C<sub>1-10</sub> straight chain alkyl, C<sub>1-10</sub> branched alkyl, or C<sub>3-10</sub> cyclic or bicyclic alkyl;

50      R<sub>3</sub> is an acyl substituent selected from the group consisting of formyl, alkanoyl of 2 to 7 carbon atoms, alkenoyl of 3 to 7 carbon atoms, alkylsulfonyl of 1 to 7 carbon atoms, aroyl of 7 to 12 carbon atoms, arylalkenoyl of 9 to 20 carbon atoms, arylsulfonyl of 6 to 12 carbon atoms, arylalkanoyl of 8 to 12 carbon atoms or arylalkylsulfonyl of 7 to 12 carbon atoms;

55      A is selected from the group consisting of:



40  $R_4$  is hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> perfluoroalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> perfluoroalkoxy, amino, C<sub>1-6</sub> alkylamino, C<sub>2-12</sub> dialkylamino, C<sub>1-6</sub> alkylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, nitro, cyano, carboxyl;

45 or, A is a phenyl group of the following formula:

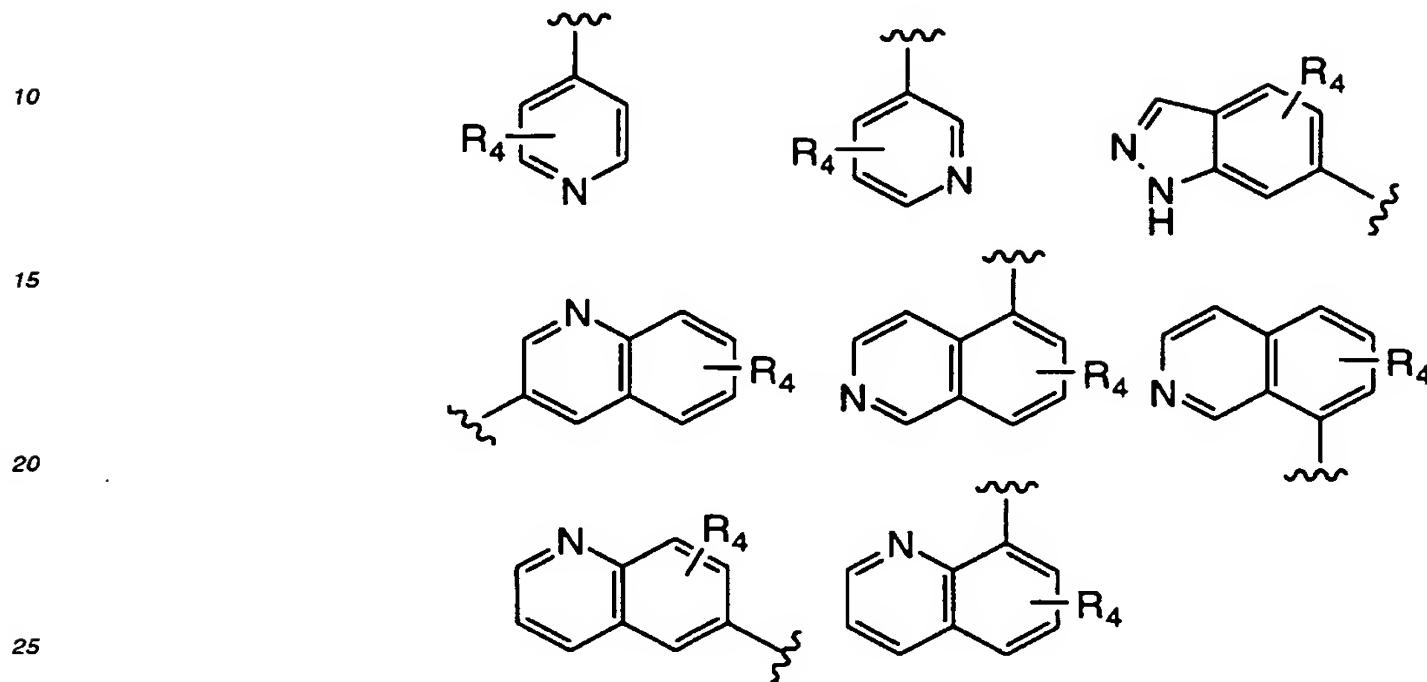


55 wherein:

55  $R_5$  and  $R_6$ , independent from each other, are selected from the following: cyano, nitro, amino, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> perfluoroalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> perfluoroalkoxy, C<sub>1-6</sub> alkylamino, C<sub>2-12</sub> dialkylamino, sulfamyl, C<sub>1-6</sub> alkylsulfonamido, C<sub>6-12</sub> arylsulfonamido, alkylcarboxamido containing 2 to 7 carbon atoms, arylcarboxamido containing 7 to 13 carbon atoms, C<sub>2-6</sub> alkanoyl, C<sub>1-6</sub> alkylsulfonyl, C<sub>1-6</sub> perfluoroalkylsul-

fonyl, C<sub>6-12</sub> arylsulfonyl, chloro, bromo, fluoro, iodo, 1-imidazolyl, carboxyl or hydrogen; or a pharmaceutically acceptable salt thereof.

5 2. A compound of Claim 1 in which A is selected from the following:



wherein:

30 R<sub>4</sub> is as defined in Claim 1;

or, A is a phenyl group of the following formula:



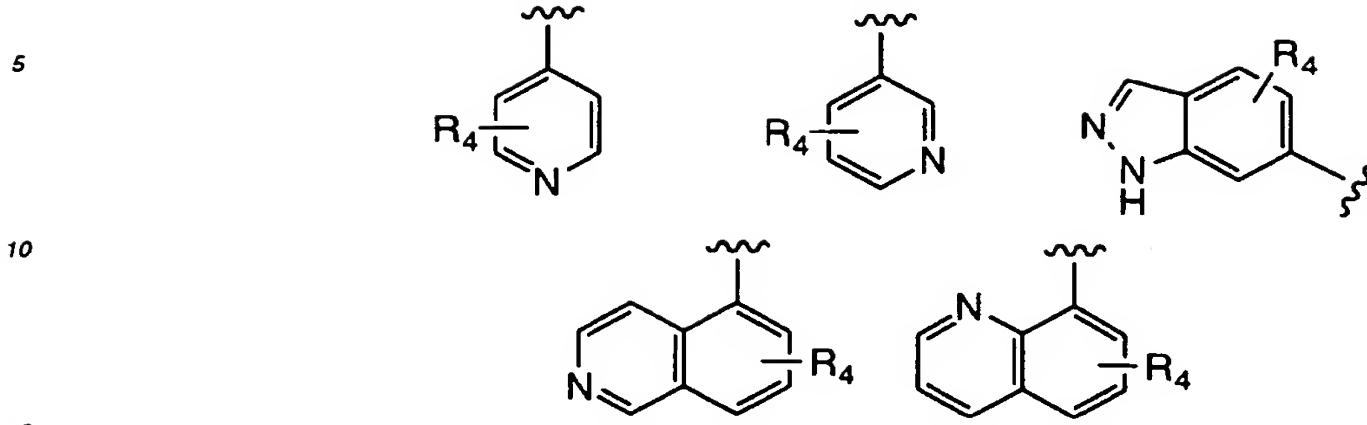
wherein:

45 R<sub>5</sub> and R<sub>6</sub>, independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, perfluoroalkyl of 1 to 6 carbon atoms, alkanoyl of 2 to 6 carbon atoms, carboxyl or hydrogen;

50 or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 in which A is selected from the following:

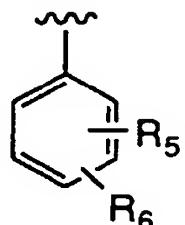
55



wherein:

20  $R_4$  is as defined in Claim 1;

25 or, A is a phenyl group of the following formula:



wherein:

35  $R_5$  and  $R_6$ , independent from each other, are selected from the following: cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, perfluoroalkyl of 1 to 6 carbon atoms, alkanoyl of 2 to 6 carbon atoms, carboxyl or hydrogen;

40 or a pharmaceutically acceptable salt thereof.

45 4. 3-Alkylamino-4-[(substituted phenyl)amino]-cyclobut-3-ene-1,2-dione in which said alkyl group contains 1 to 6 carbon atoms and the phenyl group is substituted by one or two members selected from the group consisting of cyano, nitro, amino, halo, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, trifluoroalkyl of 1 to 6 carbon atoms, alkanoyl of 2 to 6 carbon atoms, and carboxyl groups, and the amino group in 4-position of the cyclobut-3-ene-1,2-dione is substituted with a member of the group consisting of alkylcarbonyl of 2 to 6 carbon atoms, alkenylcarbonyl of 3 to 6 carbon atoms or arylcarbonyl of 7 to 12 carbon atoms.

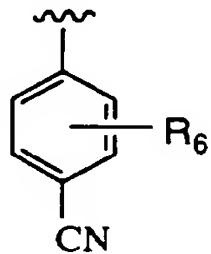
50 5. A compound of Claim 1 which is selected from N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-propionamide;

55 N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-benzamide; N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-methanesulfonamide; N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-formamide; hexanoic acid N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-amide; N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-isobutyramide; N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-phenyl-acrylamide; N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-carbamic acid ethyl ester;

5 N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide;  
 (R)-(-)-N-(4-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide;  
 N-(4-cyano-phenyl)-N-[3,4-dioxo-2-isopropylamino-cyclobut-1-enyl]-acetamide;  
 N-(4-cyano-phenyl)-N-[2-(1,2-dimethyl-propylamino)-3,4-dioxo-cyclobut-1-enyl]-acetamide;  
 N-(3-cyano-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide;  
 (R)-N-(4-cyano-phenyl)-N-[2-(1-cyclohexyl-ethylamino)-3,4-dioxo-cyclobut-1-enyl]-acetamide;  
 N-(2-butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(4-cyano-phenyl)-acetamide;  
 N-(endo)-[2-(bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enyl]-N-(4-cyano-phenyl)-acetamide;  
 N-(2-tert-butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(isoquinolin-5-yl)-acetamide;  
 N-(2-tert-butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(pyridin-3-yl)-acetamide;  
 10 N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-N-(2-methoxy-5-trifluoromethyl-phenyl)-acetamide;  
 (endo)-N-[2-(bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-enyl]-N-(pyridin-4-yl)-acetamide;  
 15 N-(2-sec-butylamino-3,4-dioxo-cyclobut-1-enyl)-N-(4-cyano-phenyl)-acetamide;  
 N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-N-(pyridin-3-yl)-acetamide;  
 N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-3-methyl-N-(pyridin-4-yl)-butyramide and  
 N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-N-(pyridin-4-yl)-pentylamide.

20 6. A compound of Claim 1 in which A is

25

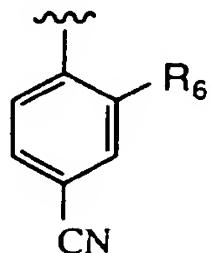


30

where R6 is alkyl of 1 to 3 carbon atoms, chloro, bromo, fluoro or iodo, or a pharmaceutically acceptable salt thereof.

35 7. A compound of Claim 1 in which A is

40



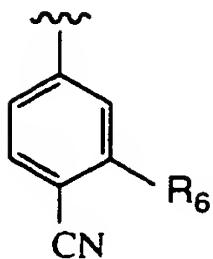
45

where R6 is alkyl of 1 to 3 carbon atoms,  
 or a pharmaceutically acceptable salt thereof.

50 8. A compound of Claim 1 in which A is

55

5



10

where R<sub>6</sub> is chloro, bromo, fluoro or iodo,  
or a pharmaceutically acceptable salt thereof.

15 9. A compound of Claim 1 which is N-(4-cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cy-  
clobut-1-enyl]-butyramide or a pharmaceutically acceptable salt thereof.

10. A compound of Claim 1 which is N-(4-cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl -propylamino)-cy-  
clobut-1-enyl]-propionamide or a pharmaceutically acceptable salt thereof.

20 11. A compound of Claim 1 which is N-(4-cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-  
1-enyl]-crotonamide or a pharmaceutically acceptable salt thereof.

25 12. A compound of Claim 1 which is selected from N-(4-cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-pro-  
pylamino)-cyclobut-1-enyl]-acetamide;

N-(4-cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-pentanamide;  
N-(4-cyano-2-ethyl-phenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-cyclohexanecar-  
boxamide;

30 N-(3-chloro-4-cyano-phenyl)-N-[3,4 dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamide and  
their pharmaceutically acceptable salts thereof.

13. Use of a compound as claimed in any one of Claims 1 to 12 to make a medicament for reducing the adverse effects  
of smooth muscle contractions.

35 14. Use of a compound as claimed in any one of Claims 1 to 12 to make a medicament for treating urinary incontinence.

15. Use of a compound as claimed in any one of Claims 1 to 12 to make a medicament for treating irritable bowel  
syndrome.

40 16. A compound as claimed in any one of claims 1 to 12 for use as a pharmaceutical.

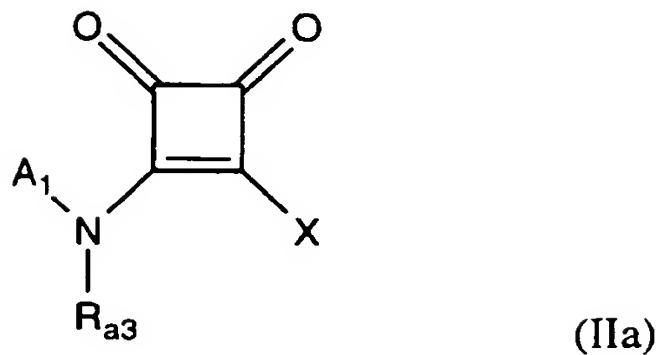
17. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 12 in combination or  
association with a pharmaceutically acceptable carrier.

45 18. A process for preparation of a compound as claimed in Claim 1, which comprises reaction of a compound having  
the formula (IIa):

50

55

5

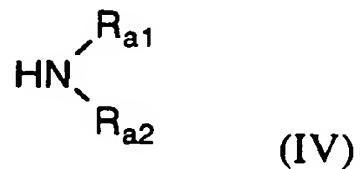


10

15

wherein X is a leaving group, for example, methoxy, ethoxy, isopropoxy, halogen or a similar leaving group and A<sub>1</sub> is A and R<sub>a3</sub> is R<sub>3</sub>, as defined hereinbefore or a group of atoms convertible thereto, with a compound of formula (IV):

20



25

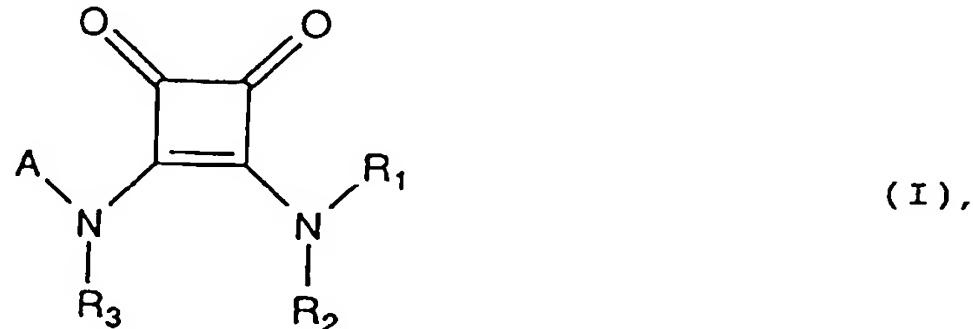
wherein R<sub>a1</sub> and R<sub>a2</sub> are R<sub>1</sub> and R<sub>2</sub>, respectively, as defined hereinbefore or a group of atoms convertible thereto and, where appropriate, converting A<sub>1</sub> into A or converting R<sub>a1</sub> into R<sub>1</sub> or converting R<sub>a2</sub> into R<sub>2</sub>, followed by reacylation if necessary and, where desired, converting a compound having formula (I) into a pharmaceutically acceptable salt thereof or converting a salt of a compound having formula (I) into a compound having formula (I).

#### Patentansprüche

35

1. Verbindung der Formel:

40



45

worin:

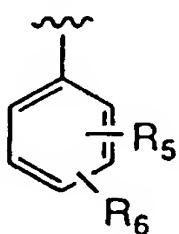
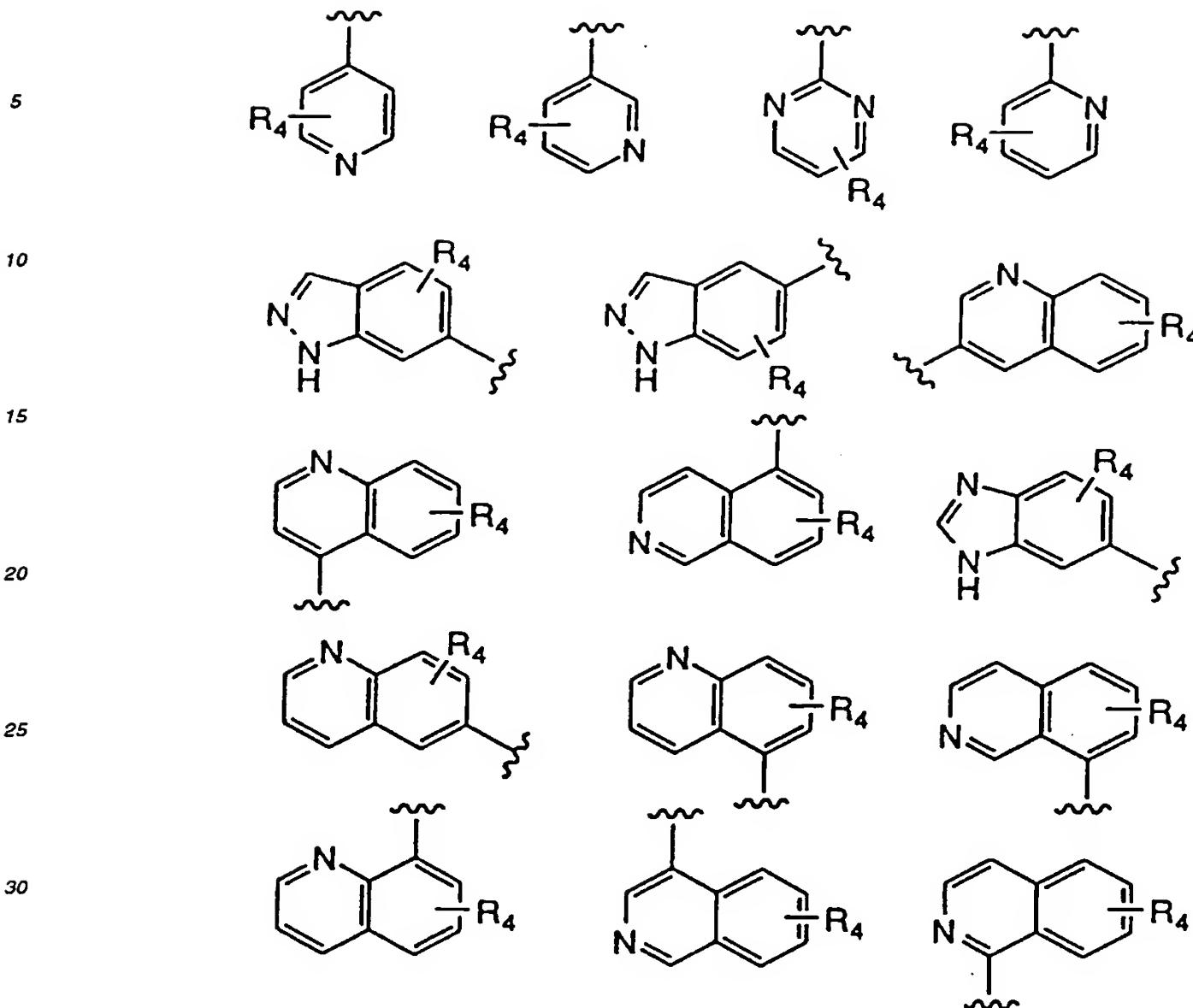
50

R<sub>1</sub> und R<sub>2</sub> unabhängig voneinander Wasserstoff, geradkettiges C<sub>1</sub>-C<sub>10</sub>-Alkyl, verzweigtes C<sub>1</sub>-C<sub>10</sub>-Alkyl, oder cyclisches oder bicyclisches C<sub>3</sub>-C<sub>10</sub>-Alkyl bedeuten;

55

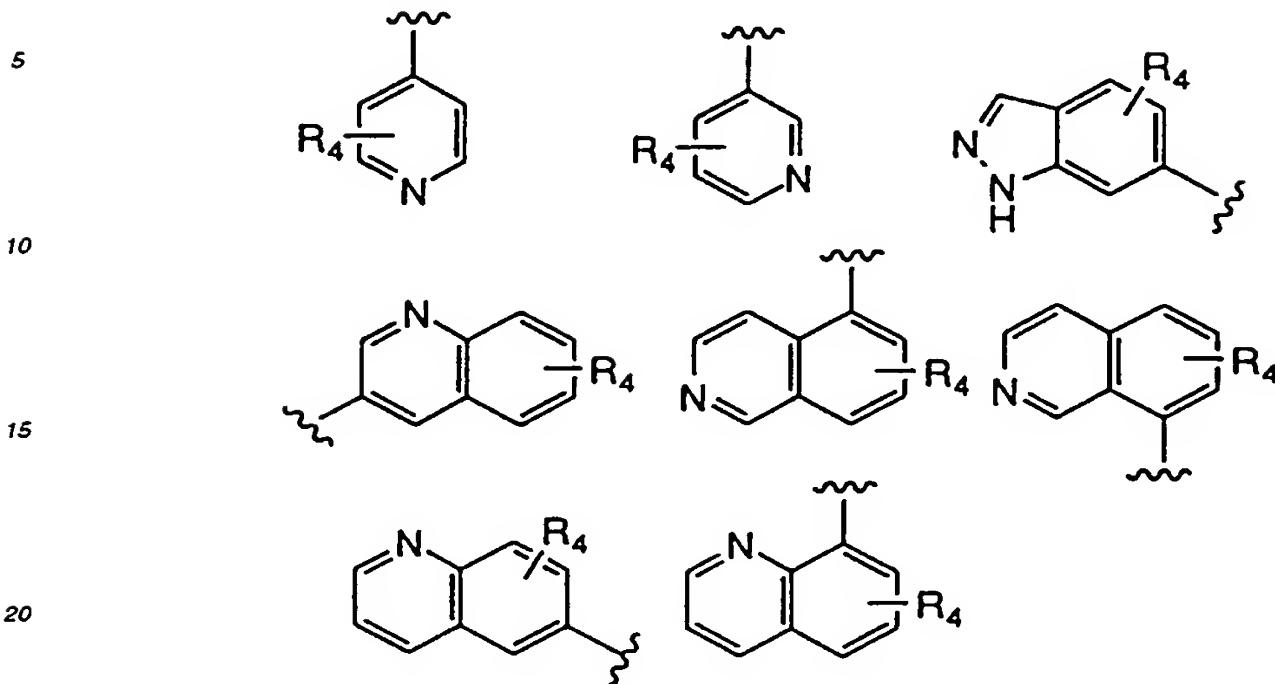
R<sub>3</sub> einen Acyl-Substituenten darstellt, ausgewählt aus der Gruppe bestehend aus Formyl, Alkanoyl mit 2 bis 7 Kohlenstoffatomen, Alkenoyl mit 3 bis 7 Kohlenstoffatomen, Alkylsulfonyl mit 1 bis 7 Kohlenstoffatomen, Aroyl mit 7 bis 12 Kohlenstoffatomen, Arylalkenoyl mit 9 bis 20 Kohlenstoffatomen, Arylsulfonyl mit 6 bis 12 Kohlenstoffatomen, Arylalkanoyl mit 8 bis 12 Kohlenstoffatomen oder Arylalkylsulfonyl mit 7 bis 12 Kohlenstoffatomen;

A ausgewählt ist aus der Gruppe bestehend aus:



oder ein pharmazeutisch annehmbaren Salz hiervon.

2. Verbindung nach Anspruch 1, worin A ausgewählt ist aus den folgenden:

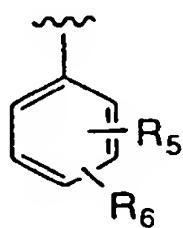


25 worin:

R<sub>4</sub> wie in Anspruch 1 definiert ist;  
oder A eine Phenylgruppe der folgenden Formel darstellt:

30

35



worin:

40 R<sub>5</sub> und R<sub>6</sub> unabhängig voneinander ausgewählt sind aus den folgenden: Cyano, Nitro, Amino, Chlor, Brom, Fluor, Iod, 1-Imidazolyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Perfluoralkyl mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen, Carboxyl oder Wasserstoff;

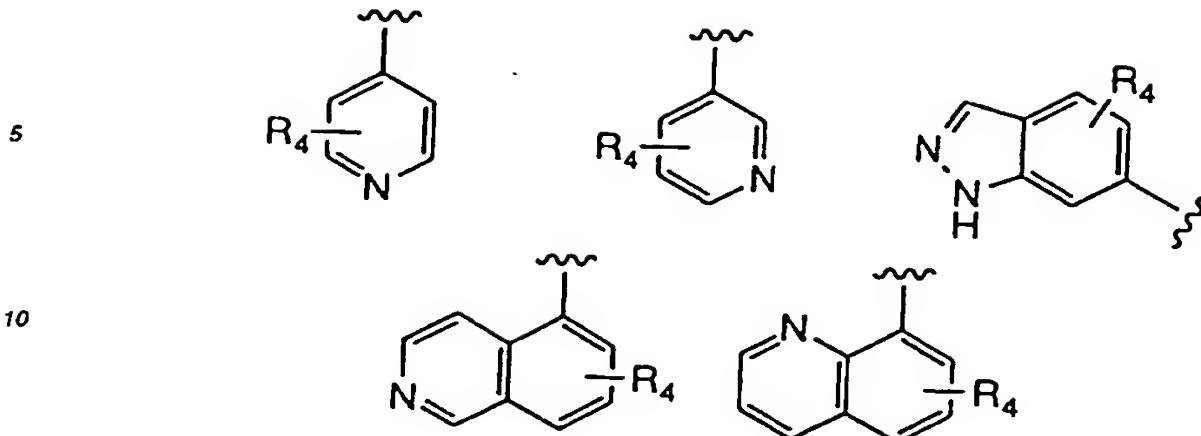
oder ein pharmazeutisch annehmbares Salz hiervon.

45

3. Verbindung nach Anspruch 1, worin A ausgewählt ist aus den folgenden:

50

55

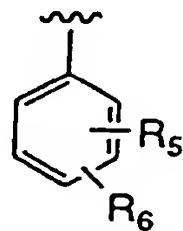


worin:

R<sub>4</sub> wie in Anspruch 1 definiert ist;  
oder A eine Phenylgruppe der folgenden Formel darstellt:

20

25



30

worin:

R<sub>5</sub> und R<sub>6</sub> unabhängig voneinander ausgewählt sind aus den folgenden: Cyano, Nitro, Amino, Chlor, Brom, Fluor, Iod, 1-Imidazolyl, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Perfluoralkyl mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen, Carboxyl oder Wasserstoff;

35

oder ein pharmazeutisch annehmbares Salz hiervon.

40

4. 3-Alkylamino-4-[(substituiertes Phenyl)-amino]-cyclobut-3-en-1,2-dion, worin die Alkyl-Gruppe 1 bis 6 Kohlenstoffatome enthält, und die Phenyl-Gruppe substituiert ist durch ein oder zwei Mitglieder, ausgewählt aus der Gruppe bestehend aus Cyano, Nitro, Amino, Halogen, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy mit 1 bis 6 Kohlenstoffatomen, Trifluoralkyl mit 1 bis 6 Kohlenstoffatomen, Alkanoyl mit 2 bis 6 Kohlenstoffatomen und Carboxyl-Gruppen, und die Amino-Gruppe in Stellung 4 des Cyclobut-3-en-1,2-dions substituiert ist mit einem Mitglied der Gruppe bestehend aus Alkylcarbonyl mit 2 bis 6 Kohlenstoffatomen, Alkenylcarbonyl mit 3 bis 6 Kohlenstoffatomen oder Arylcarbonyl mit 7 bis 12 Kohlenstoffatomen.

45

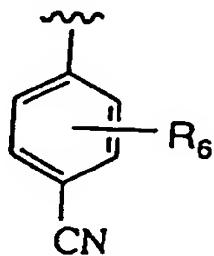
5. Verbindung nach Anspruch 1, welche ausgewählt ist aus:

50

N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropyl-amino)-cyclobut-1-enyl]-propionamid;  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropyl-amino)-cyclobut-1-enyl]-benzamid;  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropyl-amino)-cyclobut-1-enyl]-methansulfonamid;  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropyl-amino)-cyclobut-1-enyl]-formamid;  
Hexansäure, N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-amid,  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropyl-amino)-cyclobut-1-enyl]-isobutyramid;  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropyl-amino)-cyclobut-1-enylamino]-3-phenylacrylamid;  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enylamino]-carbamidsäureethylester;  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-acetamid;  
(R)-(-)-N-(4-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-acetamid;  
N-(4-Cyanophenyl)-N-[3,4-dioxo-2-isopropylaminocyclobut-1-enyl]-acetamid;

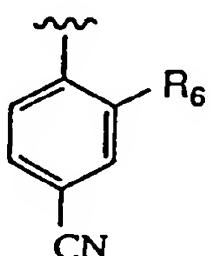
5      N-(4-Cyanophenyl)-N-[2-(1,2-dimethylpropylamino)-3,4-dioxo-cyclobut-1-enyl]-acetamid;  
 N-(3-Cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-acetamid;  
 (R)-N-(4-Cyanophenyl)-N-[2-(1-cyclohexylethylamino)-3,4-dioxocyclobut-1-enyl]-acetamid;  
 N-(2-Butylamino-3,4-dioxocyclobut-1-enyl)-N-(4-cyano-phenyl)-acetamid;  
 N-(endo)-[2-(Bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxocyclobut-1-enyl]-N-(4-cyanophenyl)-acetamid;  
 N-(2-tert-Butylamino-3,4-dioxocyclobut-1-enyl)-N-(isochinolin-5-yl)-acetamid;  
 N-(2-tert-Butylamino-3,4-dioxocyclobut-1-enyl)-N-(pyridin-3-yl)-acetamid;  
 N-[3,4-Dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-N-(2-methoxy-5-trifluormethylphenyl)-acet-  
 amid;  
 10     (endo)-N-[2-(Bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxocyclobut-1-enyl]-N-(pyridin-4-yl)-acetamid;  
 N-(2-sec-Butylamino-3,4-dioxocyclobut-1-enyl)-N-(4-cyanophenyl)-acetamid;  
 N-[3,4-Dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-N-(pyridin-3-yl)-acetamid;  
 N-[3,4-Dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-N-(pyridin-4-yl)-acetamid;  
 15     N-[3,4-Dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-3-methyl-N-(pyridin-4-yl)-butyramid und  
 N-[3,4-Dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-N-(pyridin-4-yl)-pentylamid.

6. Verbindung nach Anspruch 1, worin A bedeutet:



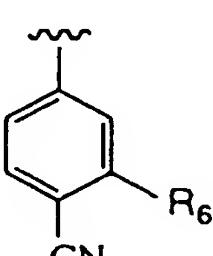
wobei R<sub>6</sub> Alkyl mit 1 bis 3 Kohlenstoffatomen, Chlor, Brom, Fluor oder Iod darstellt, oder ein pharmazeutisch annehmbares Salz hiervon.

30     7. Verbindung nach Anspruch 1, worin A bedeutet:



wobei R<sub>6</sub> Alkyl mit 1 bis 3 Kohlenstoffatomen darstellt, oder ein pharmazeutisch annehmbares Salz hiervon.

45     8. Verbindung nach Anspruch 1, worin A bedeutet:



55     wobei R<sub>6</sub> Chlor, Brom, Fluor oder Iod darstellt, oder ein pharmazeutisch annehmbares Salz hiervon.

9. Verbindung nach Anspruch 1, nämlich N-(4-Cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cyclobut-1-enyl]-butyramid oder ein pharmazeutisch annehmbares Salz hiervon.

10. Verbindung nach Anspruch 1, nämlich N-(4-Cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cy-  
clobut-1-enyl]-propionamid oder ein pharmazeutisch annehmbares Salz hieron.

11. Verbindung nach Anspruch 1, nämlich N-(4-Cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethylpropylamino)-cy-  
clobut-1-enyl]-crotonamid oder ein pharmazeutisch annehmbares Salz hieron.

12. Verbindung nach Anspruch 1, welche ausgewählt ist aus:

10 N-(4-Cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamid;  
N-(4-Cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-pentanamid;  
N-(4-Cyano-2-ethylphenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-cyclohexancar-  
boxamid;  
N-(3-Chlor-4-cyanophenyl)-N-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enyl]-acetamid

15 und ihren pharmazeutisch annehmbaren Salzen.

13. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur  
Verringerung der nachteiligen Wirkungen von Kontraktionen glatter Muskeln.

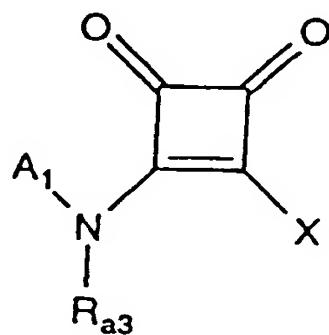
20 14. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur  
Behandlung von Harninkontinenz.

15. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 12 bei der Herstellung eines Medikaments zur  
Behandlung von Reizkolon.

25 16. Verbindung nach einem der Ansprüche 1 bis 12 zur Verwendung als Pharmazeutikum.

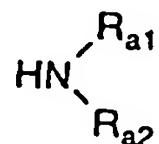
17. Pharmazeutische Zusammensetzung, welche eine Verbindung nach einem der Ansprüche 1 bis 12 in Kombination  
oder Assoziation mit einem pharmazeutisch annehmbaren Träger umfaßt.

30 18. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, welches umfaßt: Umsetzen einer Verbindung der  
Formel (IIa):



(IIa),

45 worin X eine Abgangsgruppe bedeutet, beispielsweise Methoxy, Ethoxy, Isopropoxy, Halogen oder eine ähnliche  
Abgangsgruppe, und A<sub>1</sub> A darstellt, und R<sub>a3</sub> R<sub>3</sub>, wie vorstehend definiert, oder eine in diese überführbare Atom-  
gruppe ist, mit einer Verbindung der Formel (IV):



(IV),

55 worin R<sub>a1</sub> und R<sub>a2</sub> R<sub>1</sub> bzw. R<sub>2</sub>, wie vorstehend definiert, oder eine in diese überführbare Atomgruppe bedeuten,  
und, wenn geeignet, Überführen von A<sub>1</sub> in A, oder Überführen von R<sub>a1</sub> in R<sub>1</sub>, oder Überführen von R<sub>a2</sub> in R<sub>2</sub>.

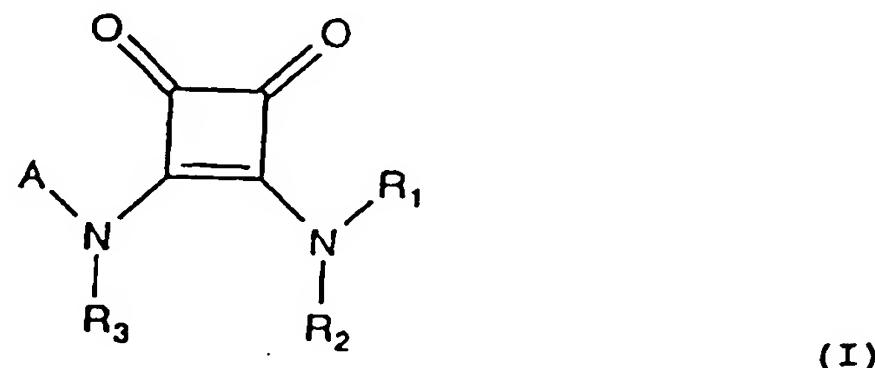
gefolgt von Reacylierung, wenn notwendig, und, wenn gewünscht, Überführen einer Verbindung der Formel (I) in ein pharmazeutisch annehmbares Salz hievon, oder Überführen eines Salzes einer Verbindung der Formel (I) in eine Verbindung der Formel (I).

5

**Revendications**

1. Composé de formule :

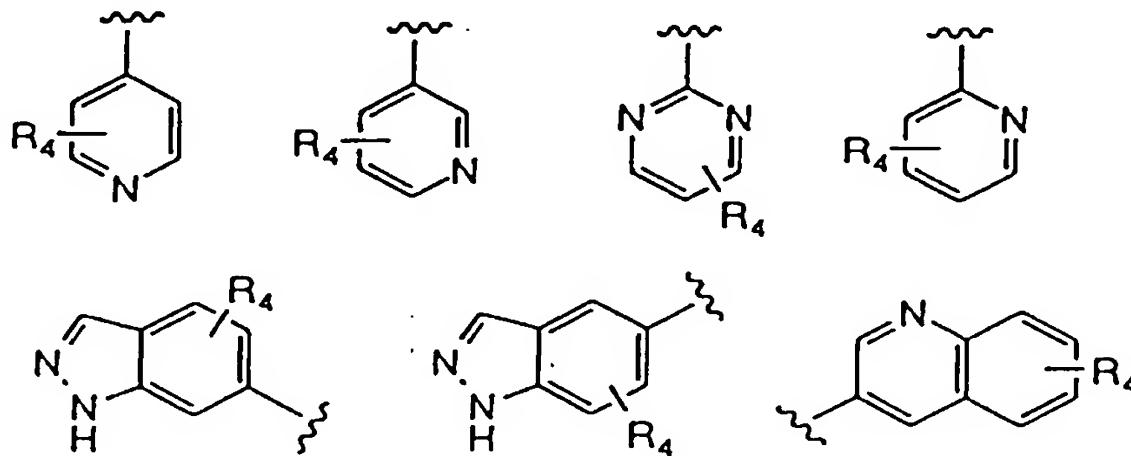
10



dans laquelle

25  $R_1$  et  $R_2$  sont, indépendamment l'un de l'autre, un atome d'hydrogène, un radical alcoyle en  $C_{1-10}$  à chaîne droite, alcoyle en  $C_{1-10}$  à chaîne ramifiée ou alcoyle en  $C_{3-10}$  cyclique ou bicyclique;  
 $R_3$  est un substituant acyle choisi parmi le groupe constitué des radicaux formyle, alcanoyle de 2 à 7 atomes de carbone, alcénoyle de 3 à 7 atomes de carbone, alcoylsulfonyle de 1 à 7 atomes de carbone, aroyle de 7 à 12 atomes de carbone, arylalcénoyle de 9 à 20 atomes de carbone, arylsulfonyle de 6 à 12 atomes de carbone, arylalcanoyle de 8 à 12 atomes de carbone ou arylalcoylsulfonyle de 7 à 12 atomes de carbone;  
30  $A$  est choisi parmi le groupe constitué de  
 $A$  est choisi parmi le groupe constitué de

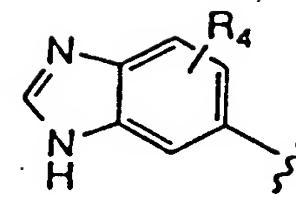
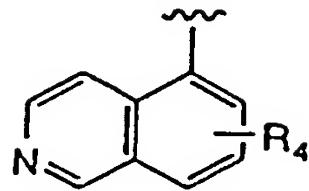
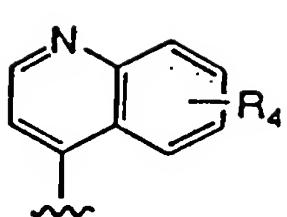
35



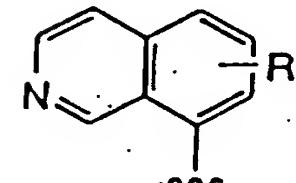
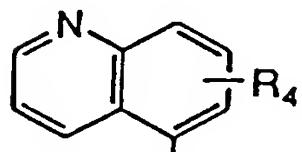
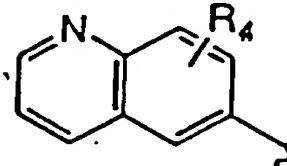
50

55

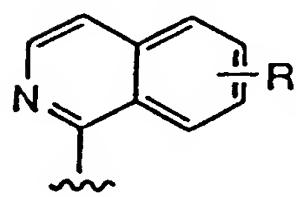
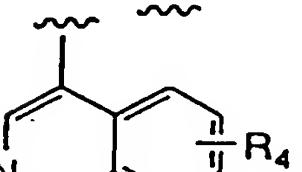
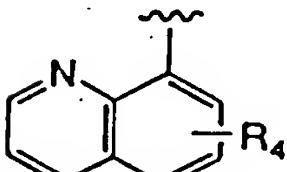
5



10



15



20

dans lequel :

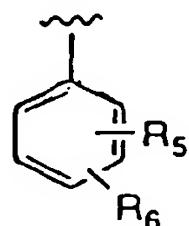
25

R<sub>4</sub> est hydrogène, alcoyle en C<sub>1-6</sub>, perfluoroalcoyle en C<sub>1-6</sub>, alcoxy en C<sub>1-6</sub>, perfluoroalcoxy en C<sub>1-6</sub>, amino, alcoylamino en C<sub>1-6</sub>, dialcoylamino en C<sub>2-12</sub>, alcoylsulfonamido en C<sub>1-6</sub>, alcoylcarboxamido contenant 2 à 7 atomes de carbone, nitro, cyano, carboxyle;

30

ou A est un radical phényle de formule suivante :

35



40

dans laquelle :

45

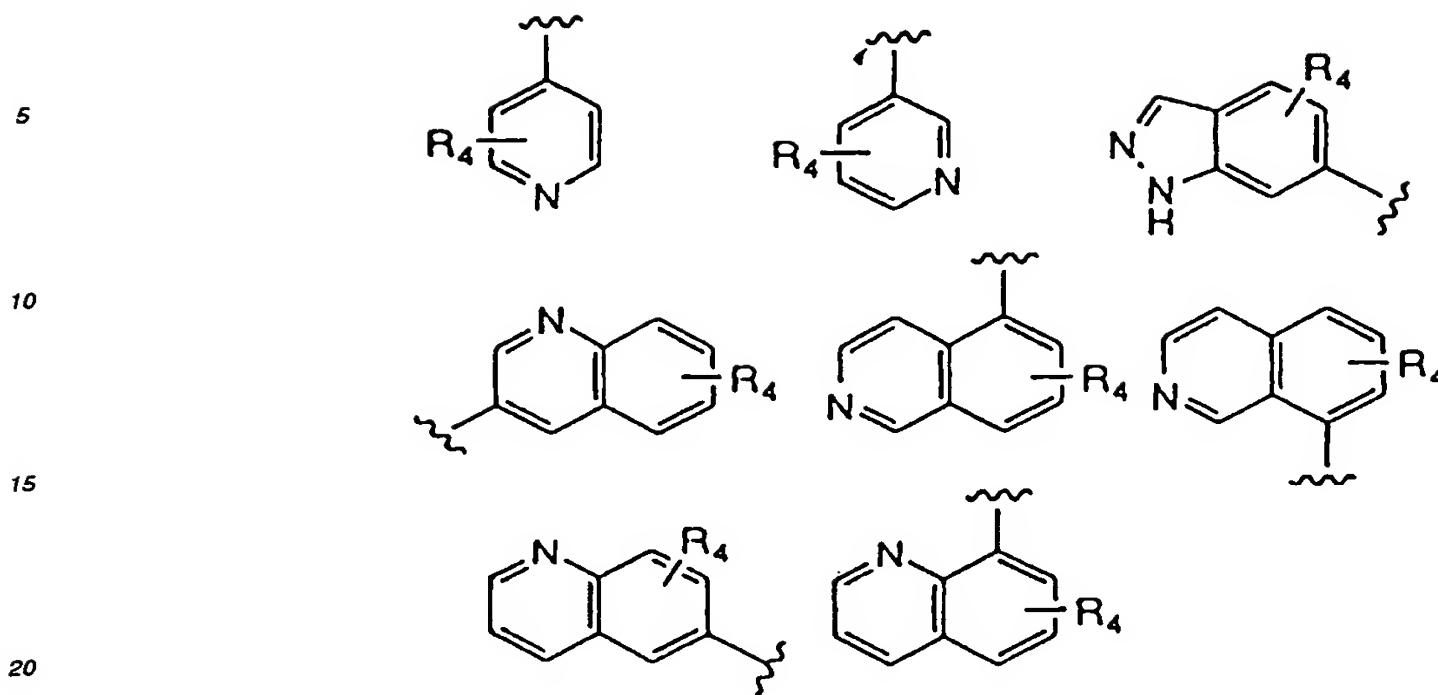
R<sub>5</sub> et R<sub>6</sub>, indépendamment l'un de l'autre, sont choisis parmi les radicaux suivants : cyano, nitro, amino, alcoyle en C<sub>1-6</sub>, perfluoroalcoyle en C<sub>1-6</sub>, alcoxy en C<sub>1-6</sub>, perfluoroalcoxy en C<sub>1-6</sub>, alcoylamino en C<sub>1-6</sub>, dialcoylamino en C<sub>2-12</sub>, sulfamyle, alcoylsulfonamido en C<sub>1-6</sub>, arylsulfonamido en C<sub>6-12</sub>, alcoylcarboxamido contenant 2 à 7 atomes de carbone, arylcarboxamido contenant 7 à 13 atomes de carbone, alcanoyle en C<sub>2-6</sub>, alcoylsulfonyle en C<sub>1-6</sub>, perfluoroalcoylsulfonyle en C<sub>1-6</sub>, arylsulfonyle en C<sub>6-12</sub>, chloro, bromo, fluoro, iodo, 1-imidazolyde, carboxyle ou hydrogène;

50

ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1 dans lequel A est choisi parmi les suivants :

55



dans lequel :

25  $R_4$  est tel que défini dans la revendication 1;  
ou  $A$  est un radical phényle de formule suivante ;



40 dans laquelle :

35  $R_5$  et  $R_6$ , indépendamment l'un de l'autre, sont choisis parmi les radicaux suivants : cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyle, alcoyle de 1 à 6 atomes de carbone, alcoxy de 1 à 6 atomes de carbone, perfluoroalcoyle de 1 à 6 atomes de carbone, alcanoyle de 2 à 6 atomes de carbone, carboxyle ou hydrogène;

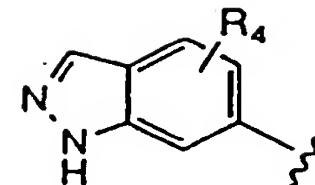
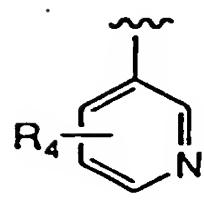
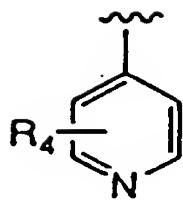
45 ou un sel pharmaceutiquement acceptable de celui-ci.

3. Composé selon la revendication 1 dans lequel  $A$  est choisi parmi les suivants :

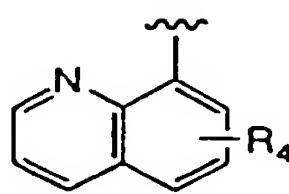
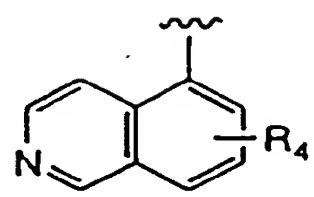
50

55

5



10

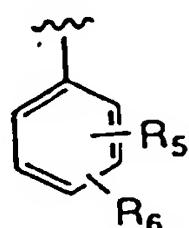


15

dans laquelle :

R<sub>4</sub> est tel que défini dans la revendication 1;  
 ou A est un radical phényle de formule suivante :

20



25

dans laquelle :

R<sub>5</sub> et R<sub>6</sub>, indépendamment l'un de l'autre, sont choisis parmi les radicaux suivants : cyano, nitro, amino, chloro, bromo, fluoro, iodo, 1-imidazolyle, alcoyle de 1 à 6 atomes de carbone, alcoxy de 1 à 6 atomes de carbone, perfluoroalcoyle de 1 à 6 atomes de carbone, alcanoyle de 2 à 6 atomes de carbone, carboxyle 35 ou hydrogène;

ou un sel pharmaceutiquement acceptable de celui-ci.

4. 3-Alcoylamino-4-[(phényle substitué)amino]-cyclobut-3-ène-1,2-dione dans laquelle ledit radical alcoyle contient 40 1 à 6 atomes de carbone et le radical phényle est substitué par un ou deux membres choisis parmi le groupe constitué des radicaux cyano, nitro, amino, halo, alcoyle de 1 à 6 atomes de carbone, alcoxy de 1 à 6 atomes de carbone, trifluoroalcoyle de 1 à 6 atomes de carbone, alcanoyle de 2 à 6 atomes de carbone, et des radicaux carboxyle, et le radical amino en position 4 de la cyclobut-3-ène-1,2-dione est substitué par un membre du groupe constitué d'alcoylcarbonyle de 2 à 6 atomes de carbone, alcénylcarbonyle de 3 à 6 atomes de carbone ou arylcarbonyle de 7 à 12 atomes de carbone.

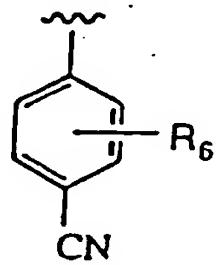
45 5. Composé selon la revendication 1, qui est choisi parmi

- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-propionamide;
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-benzamide;
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-méthanesulfonamide;
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-formamide;
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-amide de l'acide hexanoïque;
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-isobutyramide;
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-énylamino]-3-phénylacrylamide;
- l'ester éthylique de l'acide N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényla-

mino]-carbamique;

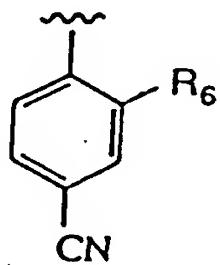
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-acétamide;
- le (R)-(-)-N-(4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-acétamide;
- le N-(4-cyanophényl)-N-[3,4-dioxo-2-isopropylamino)-cyclobut-1-ényl]-acétamide;
- le N-(4-cyanophényl)-N-[2-(1,2-diméthylpropylamino)-3,4-dioxocyclobut-1-ényl]-acétamide;
- le N-(3-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-acétamide;
- le (R)-N-(4-cyanophényl)-N-[2-(1-cyclohexyléthylamino)-3,4-dioxocyclobut-1-ényl]-acétamide;
- le N-(2-butylamino-3,4-dioxocyclobut-1-ényl)-N-(4-cyanophényl)-acétamide;
- le N-(endo)-[2-(bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-ényl]-N-(4-cyanophényl)-acétamide;
- le N-(2-t-butylamino-3,4-dioxocyclobut-1-ényl)-N-(isoquinolin-5-yl)-acétamide;
- le N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-N-(2-méthoxy-5-trifluorométhylphényl)-acétamide;
- le (endo)-N-[2-(bicyclo[2.2.1]hept-2-ylamino)-3,4-dioxo-cyclobut-1-ényl]-N-(pyridin-4-yl)-acétamide;
- le N-(2-s-butylamino-3,4-dioxocyclobut-1-ényl)-N-(4-cyanophényl)-acétamide;
- le N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-N-(pyridin-3-yl)-acétamide;
- le N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-3-méthyl-N-(pyridin-4-yl)-butyramide et
- le N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-N-(pyridin-4-yl)-pentylamide.

6. Composé selon la revendication 1 dans lequel A est



35 où R<sub>6</sub> est un radical alcoyle de 1 à 3 atomes de carbone, chloro, bromo, fluoro ou iodo,  
ou un sel pharmaceutiquement acceptable de celui-ci.

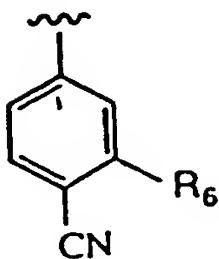
7. Composé selon la revendication 1 dans lequel A est



50 où R<sub>6</sub> est un radical alcoyle de 1 à 3 atomes de carbone,  
ou un sel pharmaceutiquement acceptable de celui-ci.

8. Composé selon la revendication 1 dans lequel A est

55



où R<sub>6</sub> est un radical chloro, bromo, fluoro ou iodo,  
ou un sel pharmaceutiquement acceptable de celui-ci.

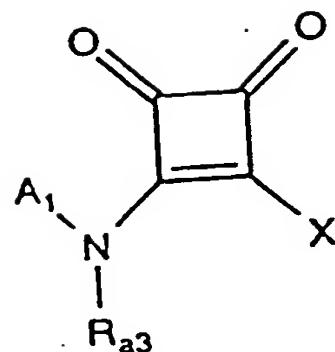
15

9. Composé selon la revendication 1 qui est le N-(4-cyano-2-éthylphényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-butyramide ou un sel pharmaceutiquement acceptable de celui-ci.
10. Composé selon la revendication 1 qui est le N-(4-cyano-2-éthylphényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-propionamide ou un sel pharmaceutiquement acceptable de celui-ci.
11. Composé selon la revendication 1 qui est le N-(4-cyano-2-éthylphényl)-N-[3,4-dioxo-2-(1,2,2-triméthyl-propylamino)-cyclobut-1-ényl]-crotonamide ou un sel pharmaceutiquement acceptable de celui-ci.
- 25 12. Composé selon la revendication 1 qui est choisi parmi
  - le N-(4-cyano-2-éthylphényl)-N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-acétamide;
  - le N-(4-cyano-2-éthylphényl)-N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-pentanamide;
  - 30 le N-(4-cyano-2-éthylphényl)-N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-cyclohexane-carboxamide;
  - le N-(3-chloro-4-cyanophényl)-N-[3,4-dioxo-2-(1,2,2-triméthylpropylamino)-cyclobut-1-ényl]-acétamide et leurs sels pharmaceutiquement acceptables.
- 35 13. Utilisation d'un composé selon l'une quelconque des revendications 1 à 12 pour fabriquer un médicament pour réduire les effets adverses des contractions des muscles lisses.
14. Utilisation d'un composé selon l'une quelconque des revendications 1 à 12 pour fabriquer un médicament pour traiter l'incontinence urinaire.
- 40 15. Utilisation d'un composé selon l'une quelconque des revendications 1 à 12 pour fabriquer un médicament pour traiter le syndrome de l'intestin irritable.
16. composé selon l'une quelconque des revendications 1 à 12 pour l'utilisation comme produit pharmaceutique.
- 45 17. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 12 en combinaison ou association avec un support pharmaceutiquement acceptable.
18. Procédé pour la préparation d'un composé selon la revendication 1, qui comprend la réaction d'un composé ayant la formule (IIa) :

50

5

10

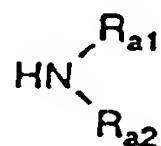


(IIa)

15

dans laquelle X est un radical partant, par exemple, un radical méthoxy, éthoxy, isopropoxy, halogène ou un radical partant similaire et A<sub>1</sub> est A et R<sub>a3</sub> est R<sub>3</sub>, comme défini ci-avant ou un radical d'atomes convertible en celui-ci, avec un composé de formule (IV) :

20



(IV)

25

30

dans laquelle R<sub>a1</sub> et R<sub>a2</sub> sont R<sub>1</sub> et R<sub>2</sub>, respectivement, comme défini ci-avant ou un radical d'atomes convertibles en ceux-ci et, si approprié, en convertissant A<sub>1</sub> en A ou en convertissant R<sub>a1</sub> en R<sub>1</sub> ou en convertissant R<sub>a2</sub> en R<sub>2</sub>, puis par réacylation si nécessaire et, si approprié, en convertissant un composé ayant la formule (I) en un sel pharmaceutiquement acceptable de celui-ci ou en convertissant un sel d'un composé ayant la formule (I) en un composé ayant la formule (I).

35

40

45

50

55